Renal Transplant
Immunosuppression

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Helderman’s Laws of Immunosuppression
Law Number One:

The longer it stays in, the longer it stays in!
Law Number Two:

Enough early, Less late
Law Number Three:

A Kidney Transplant is a Kidney
Law Number Four:

A person with a Kidney Transplant is a person
Vanderbilt’s Results


Graft Survival 96.5% (1 year)
Patient Survival 98.5% (1 year)
Acute Rejection Rate 7.5% (1 year)
Standard Regimen of Immunosuppression for Renal Transplantation

It doesn’t exist!
Three Time Periods

- Induction – Peri Operative Algorithm
- Early Maintenance – Weeks to Months
- Chronic Maintenance
Induction

- Antibody Induction
- Calcineurin Inhibitor Induction
- Sirolimus Induction
Vanderbilt’s Induction Strategy

**Low Immunologic Risk:**
Anti CD 24 antibody induction, early Calcineurin I introduction

**High Immunologic Risk - Redos, High PRA, AA**
Polyclonal Anti T-Cell AB, CI use when Creat 3.0 or less.
Minimum of 5 days of AB
Obtain therapeutic CI level before stopping AB

**Delayed Graft Survival – High Expectations or Presence**
Start with or switch to Polyclonal or Induce with Sirolimus/MMF and avoid AB and CI

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Early Maintenance Depends on Induction and Assessed Immunologic Risk of the Recipient
# Choosing an Immunosuppressive Regimen: Efficacy

## Results at One Year

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Acute Rejection (%)</th>
<th>Graft Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA/steroids (AZA)</td>
<td>40-50</td>
<td>85-90</td>
</tr>
<tr>
<td>CsA/MMF/steroids</td>
<td>15-20</td>
<td>90-95</td>
</tr>
<tr>
<td>Tacrolimus/MMF/steroids</td>
<td>10-15</td>
<td>90-95</td>
</tr>
<tr>
<td>CsA/sirolimus/steroids</td>
<td>10-20</td>
<td>90-95</td>
</tr>
<tr>
<td>Add antibody</td>
<td>Fewer (?)</td>
<td>Same</td>
</tr>
</tbody>
</table>
Maintenance Immunosuppression

- “Classical immunosuppression”
- Calcineurin inhibitor based immunosuppression
- Sirolimus based immunosuppression
Maintenance Immunosuppression

“Classical Immunosuppression”

- Prednisone and Azathioprine
- Virtually no “starts” in USA on this regimen
- Many patients engrafted before 1984 with functioning transplants with still be on this regimen
- In the absence of graft difficulty, it is reasonable not to change away from the classical approach
Maintenance Immunosuppression

Calcineurin inhibitor based immunosuppression

- CSA based regimens
- TAC based regimens
Maintenance Immunosuppression

Calcineurin inhibitor based immunosuppression

CSA based regimens

- Two drugs versus three drugs – the original story
- CSA PRED AZA
- CSA PRED MMF
MMF vs AZA in Renal Transplantation: Three-Year Tricontinental Results

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Maintenance Immunosuppression

Calcineurin inhibitor based immunosuppression

TAC based immunosuppression

• Two drugs versus three:
  TAC/PRED vs TAC/PRED/AZA

• TAC/PRED/MMF

• TAC/MMF with rapid PRED taper (one week)
Potential Strategies to Address Newer Goals

Sparing Regimens

• Targeted dose reduction or drug elimination
  – Low-responder patients (defined clinically and immunologically)
  – Initiated after risk of rejection has receded

• Avoidance of drug-specific side effects

• Less risk immunologically
Maintenance Immunosuppression

Sirolimus based immunosuppression

• The marginal donor
• Delayed graft function
• Malignancy
Maintenance Immunosuppression

The Marginal Donor

Donor age >55 yr

Hx of Diabetes

Hx of high blood pressure on Rx

DGF 1) inc s creat of 0.5 in 12 hr

2) <50 cc/hr urine in first day

Shaffer et al 2002
Maintenance Immunosuppression

The Marginal Donor

Induction  Thymoglobulin (12)

Basiliximab (7)

MMF 1 gm BID

Sirolimus 10 mg x 3, then 5 mg adjusting to 10-20 ng/ml

Prednisone – Solumedrol 500mg IV then 30 mg of pred tapered to 10 mg
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Maintenance Immunosuppression

The Marginal Donor

n = 19

n = 11 DGF

6 donor age and/or comorbid disease

2 both

16 CKT

3 LD

Shaffer et al 2002

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Maintenance Immunosuppression

The Marginal Donor

Mean S creat 1.7
AR 3/19 (16%) day 4, 9, 45
No AR thymo induction
1 Lymphocele
2 Superficial wound infection
4 TAC conversions (3 AR, 1 wound)
15 RAP for chronic maintenance
Maintenance Immunosuppression

The Marginal Donor

F/U 294 d (159-666)

Pt Survival – 1 yr 100% (Actuarial)

Graft Survival – 1 yr 93% (1 primary nonfunction 4 to rejection)

Shaffer et al 2002
Delayed Graft Function: Sirolimus-Based Regimen

Average Serum Creatinine Level (mg/dL)

Initial | 30 Days | 90 Days

Calcineurin Inhibitor Minimization Regimens

- **Benefits**
  - Improved renal function
  - Reduction in other calcineurin inhibitor–associated effects (hypertension, hyperlipidemia, glucose intolerance)

- **Risks**
  - Acute Rejection; ? Chronic allograft dysfunction
Minimization of Calcineurin Inhibitors

- Facilitated by availability of non-nephrotoxic immunosuppressants
  - Mycophenolate mofetil
  - mTOR inhibitors (sirolimus, everolimus)
- Protocols
  - Dose reduction
  - Withdrawal
  - Avoidance
Calcineurin Inhibitor Avoidance

Argument For:

- Doses effective at reducing acute rejection rates to single digits too toxic.
- Activate profibrotic growth factor genes (e.g., TGFβ).
- Mechanism confined to inhibition of T cell activation.
- May delimit long term graft survival.
Calcineurin Inhibitor Avoidance

Argument For:

- “T ½ of grafts unchanged in CI era” is the mantra
- Important side effects may be avoided
  - nephrotoxicity
  - cosmetic
  - diabetogenesis
  - hyperlipidemia
  - hyperkalemia
  - hyperuricemia
  - neuro toxicity
CSA Reduction in Chronic Nephropathy

Weir and colleagues withdrew CsA and added MMF in 25 pts with bx proven CAN

1. Creatinine fell significantly
2. Cholesterol fell
3. No acute rejections were encountered

Weir et al Transplantation 64:1706, 1997
Cyclosporine Sparing Regimens

- CsA withdrawal with or without AZA substitution
- Low dose CsA in triple therapy regimens containing MMF
- Introducing new immunosuppressive drugs and reducing CsA dose
- Avoiding CNI and substituting sirolimus
Calcineurin Inhibitor Dose Reduction and/or Withdrawal With MMF (single center, CsA or FK506 withdrawn (n=18) or reduced by 50% (n=100), 1.8 years follow-up)

No CNI (n = 18)
Reduced tacrolimus (n = 33)
Reduced CsA (n = 67)

CNI = calcineurin inhibitor.
Grinyo CsA Sparing / MMF Trial

1. Under MMF umbrella, CsA dose gradually reduced
2. No acute rejections in 16 pts
3. Significant improvements in diastolic BP
4. Decreased creatinine, increased GFR
5. Reduced blood levels of TGF-β
Targeted CsA Dose Reductions when MMF Employed

Target levels: 50 - 100 ng/mL

CsA Dose (mg/kg/dl)

Years After Tx

0.25 1 3 5

GRINYO

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Safe CsA Reduction Leads to Reduced TGF-β

A

Before MMF

6 Months

P = .003

B

CsA levels (ng/mL)

TGF-β1 (platelet-free plasma) (ng/mL)

r = .536

p = .0016
Calcineurin Sparing

Prograf Sparing

Trials of MacDonald, Dalhousie Univ.

Low dose Prograf + Sirolimus

Results

- single digit acute rejection rates
- higher GFR, lower creatinines
- excellent graft & pt survival
- short follow times

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Calcineurin Inhibitor Dose Reduction and/or Withdrawal Regimens With Sirolimus

[Graph showing comparison between Sirolimus/CsA/steroids (n = 215) and Sirolimus/steroids (n = 215)]

Patients (%)

>10% Improved Serum Creatinine

>10% Improved Glomerular Filtration Rate

Use of Sirolimus to Facilitate Cyclosporine Withdrawal: Study 310

Sirolimus 2 mg + CsA 200-400 ng/ml + Steroids
> 5 ng/ml 150-300 ng/ml

Group A

3 months ± 2 weeks

Group B

Sirolimus 2 mg + CsA (25% per week) + Steroids
(>5 ng/ml)

Sirolimus (75-200 ng/ml)

Johnson RWG et al. Transplantation 2001; 72: 777
Higher Calculated GFR Following CsA Elimination

Mean Calculated GFR (Nankivell)

- Group A
- Group B

Randomization

*p<0.001
Incidence of Acute Rejection: 6 month data

<table>
<thead>
<tr>
<th></th>
<th>Prerandomization</th>
<th>Postrandomization</th>
<th>6 months (ITT)</th>
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<tbody>
<tr>
<td>Group A</td>
<td>9.3%</td>
<td>2.3%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Group B</td>
<td>9.8%</td>
<td>7.4%</td>
<td>17.2%</td>
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Vanderbilt Strategy of Early Maintenance

- **Low Risk** - CSA based triple therapy with MMF
- **Special Risk** - TAC based triple therapy with MMF
- **Under Study** - CI avoidance with RAP for high risk donors and when vasoconstriction should be avoided
Late Maintenance

General Rule – Taper Most of the elements of Early Maintenance
- Target blood levels for CI drugs change
- Reduce steroids to 0.1 mg/kg or less

Unique Issues of Late Maintenance
- Prednisone withdrawal
- CSA withdrawal
- Long term use of MMF
Vanderbilt Strategy of Chronic Maintenance

- Maintain CSA or TAC-No Withdrawal
- Maintain Low Dose Pred. 5 - 7.5mg
- Maintain Long Term MMF Use