IMMUNOSUPPRESSIVE THERAPY AFTER HEART TRANSPLANTATION

YEDAEEL HAR-ZAHAV MD
HEART TRANSPLANTATION


Half-life = 10.0 years
Conditional Half-life = 13.0 years

N=70,702

N at risk at 22 years: 33
ADULT HEART TRANSPLANTATION


All comparisons significant at p < 0.0001


Survival (%) vs Years

ISHLT

J Heart Lung Transplant 2007;26: 769-781

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Days 0-30 (N = 3,006)</th>
<th>– Days 31 Year 1 (N = 2,722)</th>
<th>– Year 1&lt; Years 3 (N = 2,135)</th>
<th>– Years 3&lt; Years 5 (N = 1,857)</th>
<th>– Years 5&lt; Years 10 (N = 4,054)</th>
<th>Years 10&lt; (N = 2,107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Allograft Vasculopathy</td>
<td>(1.7%) 52</td>
<td>(4.7%) 127</td>
<td>(14.0%) 298</td>
<td>(16.1%) 299</td>
<td>(14.3%) 581</td>
<td>(14.7%) 309</td>
</tr>
<tr>
<td>Acute Rejection</td>
<td>(6.4%) 193</td>
<td>(12.4%) 338</td>
<td>(10.3%) 220</td>
<td>(4.4%) 82</td>
<td>(1.7%) 69</td>
<td>(1.2%) 26</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>(0.1%) 2</td>
<td>(2.0%) 54</td>
<td>(4.0%) 85</td>
<td>(5.2%) 96</td>
<td>(4.8%) 195</td>
<td>(3.5%) 73</td>
</tr>
<tr>
<td>Malignancy, Other</td>
<td>(0.0%) 1</td>
<td>(2.1%) 57</td>
<td>(10.2%) 218</td>
<td>(18.3%) 340</td>
<td>(18.5%) 749</td>
<td>(18.6%) 392</td>
</tr>
<tr>
<td>CMV</td>
<td>(0.1%) 4</td>
<td>(1.2%) 34</td>
<td>(0.7%) 16</td>
<td>(0.2%) 3</td>
<td>(0.1%) 5</td>
<td>(0.0%) 1</td>
</tr>
<tr>
<td>Infection, Non-CMV</td>
<td>(13.1%) 393</td>
<td>(32.9%) 896</td>
<td>(12.9%) 276</td>
<td>(9.7%) 180</td>
<td>(10.9%) 442</td>
<td>(10.1%) 213</td>
</tr>
<tr>
<td>Primary Failure</td>
<td>(26.7%) 804</td>
<td>(7.2%) 196</td>
<td>(6.3%) 134</td>
<td>(4.4%) 81</td>
<td>(4.6%) 186</td>
<td>(2.0%) 43</td>
</tr>
<tr>
<td>Graft Failure</td>
<td>(15.1%) 453</td>
<td>(11.2%) 304</td>
<td>(17.1%) 365</td>
<td>(16.0%) 298</td>
<td>(14.3%) 579</td>
<td>(14.7%) 310</td>
</tr>
<tr>
<td>Technical</td>
<td>(7.8%) 233</td>
<td>(1.0%) 28</td>
<td>(0.8%) 17</td>
<td>(0.9%) 17</td>
<td>(0.9%) 36</td>
<td>(0.9%) 20</td>
</tr>
<tr>
<td>Other</td>
<td>(5.4%) 162</td>
<td>(6.4%) 175</td>
<td>(8.8%) 187</td>
<td>(7.9%) 147</td>
<td>(8.4%) 339</td>
<td>(8.3%) 175</td>
</tr>
<tr>
<td>Multiple Organ Failure</td>
<td>(11.8%) 356</td>
<td>(9.8%) 268</td>
<td>(5.5%) 117</td>
<td>(5.5%) 102</td>
<td>(7.6%) 309</td>
<td>(9.0%) 190</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>(0.7%) 20</td>
<td>(0.9%) 25</td>
<td>(1.7%) 36</td>
<td>(3.5%) 65</td>
<td>(5.6%) 225</td>
<td>(8.2%) 173</td>
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<tr>
<td>Pulmonary</td>
<td>(4.4%) 133</td>
<td>(4.0%) 108</td>
<td>(4.5%) 96</td>
<td>(4.6%) 85</td>
<td>(4.2%) 172</td>
<td>(4.7%) 99</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>(6.7%) 200</td>
<td>(4.1%) 112</td>
<td>(3.3%) 70</td>
<td>(3.3%) 62</td>
<td>(4.1%) 167</td>
<td>(3.9%) 83</td>
</tr>
</tbody>
</table>

*ISHLT*

J Heart Lung Transplant 2007;26: 769-781
### ADULT HEART TRANSPLANT RECIPIENTS:
Cause of Death from Leading Causes by Era


<table>
<thead>
<tr>
<th>CAUSE OF DEATH</th>
<th>DATE OF DEATH</th>
<th>Days 0-30 (N = 3,005)</th>
<th>– Days 31 Year 1 (N = 2,722)</th>
<th>– Year 1&lt; Years 3 (N = 2,135)</th>
<th>– Years 3&lt; Years 5 (N = 1,857)</th>
<th>Years – 5&lt; 10 Years (N = 4,054)</th>
<th>Years 10&lt; (N = 2,107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE REJECTION</td>
<td>1992-1997</td>
<td>(7.1%) 122</td>
<td>(14.3%) 231</td>
<td>(9.3%) 113</td>
<td>(4.4%) 41</td>
<td>(1.1%) 16</td>
<td>(1.1%) 16</td>
</tr>
<tr>
<td></td>
<td>1998-6/2006</td>
<td>(5.5%) 71</td>
<td>(9.7%) 107</td>
<td>(11.7%) 107</td>
<td>(4.4%) 41</td>
<td>(2.0%) 53</td>
<td>(2.0%) 53</td>
</tr>
<tr>
<td>CARDIAC ALLOGRAFT</td>
<td>1992-1997</td>
<td>(1.9%) 32</td>
<td>(5.1%) 83</td>
<td>(15.1%) 184</td>
<td>(20.1%) 189</td>
<td>(18.3%) 262</td>
<td>(18.3%) 262</td>
</tr>
<tr>
<td>VASCULOPATHY</td>
<td>1998-6/2006</td>
<td>(1.6%) 20</td>
<td>(4.0%) 44</td>
<td>(12.4%) 114</td>
<td>(12.0%) 110</td>
<td>(12.2%) 319</td>
<td>(12.2%) 319</td>
</tr>
<tr>
<td>GRAFT FAILURE</td>
<td>1992-1997</td>
<td>(15.0%) 258</td>
<td>(11.0%) 179</td>
<td>(16.4%) 200</td>
<td>(12.7%) 119</td>
<td>(12.1%) 174</td>
<td>(12.1%) 174</td>
</tr>
<tr>
<td></td>
<td>1998-6/2006</td>
<td>(15.2%) 195</td>
<td>(11.4%) 125</td>
<td>(18.0%) 165</td>
<td>(18.8%) 179</td>
<td>(15.5%) 405</td>
<td>(15.5%) 405</td>
</tr>
<tr>
<td>MALIGNANCY, OTHER</td>
<td>1992-1997</td>
<td>(0.1%) 1</td>
<td>(2.5%) 40</td>
<td>(9.7%) 118</td>
<td>(18.8%) 177</td>
<td>(17.9%) 257</td>
<td>(17.9%) 257</td>
</tr>
<tr>
<td></td>
<td>1998-6/2006</td>
<td>(0.0%) 0</td>
<td>(1.5%) 17</td>
<td>(10.9%) 100</td>
<td>(17.8%) 163</td>
<td>(18.8%) 492</td>
<td>(18.8%) 492</td>
</tr>
<tr>
<td>PRIMARY FAILURE</td>
<td>1992-1997</td>
<td>(29.5%) 508</td>
<td>(10.4%) 168</td>
<td>(8.6%) 105</td>
<td>(5.2%) 49</td>
<td>(6.9%) 99</td>
<td>(6.9%) 99</td>
</tr>
<tr>
<td></td>
<td>1998-6/2006</td>
<td>(23.1%) 296</td>
<td>(2.5%) 28</td>
<td>(3.2%) 29</td>
<td>(3.5%) 32</td>
<td>(3.3%) 87</td>
<td>(3.3%) 87</td>
</tr>
</tbody>
</table>

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Immunobiology of Rejection

Signal 1: MHC/peptides Recognition by TCR

Signal 2: Costimulation

Signal 3: IL-2R IL-15R

Adapted with permission from Professor Dr. Walter Land and M. Schneeberger, University of Munich, Germany.
Events Following T Cell Activation

Stimulus

Activation

Expansion

Rejection

Memory

0    0.5        1     2…   24 hours….      3-4 days…       7 days...

Immune System
Encounters the
Transplant

Hyperacute
Rejection

T Lymphocytes
Are Activated
And Make
Cytokines

T Cells
Divide

Plasma
Cells
Make
Antibody

Effector
T Cells
Attack the
Transplant

Humoral
Rejection

Immune
System
Develops
T and B
cell memory

T Lymphocytes
Are Activated
And Make
Cytokines

T Cells
Divide

Plasma
Cells
Make
Antibody

Effector
T Cells
Attack the
Transplant

Humoral
Rejection

Immune
System
Develops
T and B
cell memory
Acute Rj Symptoms

עייפות
ירידה של "ד ( 20ulators"
JVP בצלחת, ג الكريم
Gallop S3
tופלט פריקורדיאלי
עלילות חום
乗り עלית חום
אורתמיה ( על-חדירה, חדירה
הפרעות חולכת
סימני "א"ק לבר
Acute Rj - Echo

• Diastolic Dysfunction

• Systolic Dysfunction

• Wall Thickening
Biopsy - Complications

- Perforation
- Tamponade
- Arrhythmia
- TR
- Coronary-RV-Fistula
CORONARY FISTULA
FISTULA  RCA--RV
<table>
<thead>
<tr>
<th>Grade 0 R&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No rejection</th>
<th>Grade 0</th>
<th>No rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 R, mild</td>
<td>Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage</td>
<td>Grade 1, mild</td>
<td>Focal perivascular and/or interstitial infiltrate without myocyte damage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A—Focal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B—Diffuse</td>
<td></td>
</tr>
<tr>
<td>Grade 2 R, moderate</td>
<td>Two or more foci of infiltrate with associated myocyte damage</td>
<td>Grade 3, moderate</td>
<td>Multifocal infiltrate with myocyte damage</td>
</tr>
<tr>
<td>Grade 3 R, severe</td>
<td>Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis</td>
<td>Grade 4, severe</td>
<td>Diffuse infiltrate with myocyte damage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A—Focal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B—Diffuse</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Where “R” denotes revised grade to avoid confusion with 1990 scheme.

<sup>b</sup>The presence or absence of acute antibody-mediated rejection (AMR) may be recorded as AMR 0 or AMR 1, as required (see Table 3).
Grade 0 R—normal endomyocardial biopsy showing no evidence of cellular infiltration
Grade 1 R—low-power view of endomyocardial biopsy showing three focal perivascular infiltrates without myocyte damage, previously grade 1A
• Grade 1 R—both perivascular and interstitial infiltrates are present but without definite evidence of myocyte damage (previously grade 1A
Grade 1 R—diffuse mononuclear cell infiltrate with an interstitial pattern of lymphocytes between and around myocytes without associated myocyte damage

(previously grade 1B
Grade 2 R—damaging infiltrate with, myocyte damage and architectural distortion previously grade 3A
Grade 3 R—diffuse damaging infiltrates with encroachment of myocytes and disruption of normal architecture (previously grade 3B)
PERCENTAGE OF ADULT HEART TRANSPLANT RECIPIENTS TREATED FOR REJECTION IN 1ST YEAR

(Stratified by Maintenance Immunosuppression  (Transplants: January 1, 2000 - June 30, 2005

Overall: p<0.0001
18-44: p<0.0001
Male: p<0.0001

NOTE: There were 1,119 patients with cyclosporine+AZA and 138 with tacrolimus+AZA. These groups were excluded due to small numbers.

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NUMBER OF REJECTION EPISODES FOR ADULT HEART TRANSPLANT RECIPIENTS TREATED FOR REJECTION IN 1ST YEAR

(Stratified by Maintenance Immunosuppression  (Transplants: January 1, 2000 - June 30, 2005

![Graph showing average number of rejection episodes](image)

Overall: $p=0.0378$
18-44: $p=0.049$

NOTE: Cyclosporine+AZA and tacrolimus+AZA were excluded due to small numbers.

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ADULT HEART TRANSPLANTATION
Kaplan-Meier Survival Stratified by Rejection Within 1st Year

Conditional on survival to 1 year for transplants: 1/1995-6/2003

- No rejection (N=7,032)
- Rejection (N=6,336)

p < 0.0001

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J Heart Lung Transplant 2006;25:869-79
General Mechanisms of Action of Immunosuppressive Drugs

Small Molecules

• CsA, tacrolimus (FK506)
  – Inhibition of calcineurin phosphatase

• Mycophenolate mofetil (MMF)
  – Inhibition of inosine monophosphate dehydrogenase (IMPDH)

• Sirolimus
  – Inhibition of mTOR1 and 2

• Steroids
  – Pleiotropic effects including blocking activation of nuclear factor-kappa B (NF-κB)
### Available immunosuppressive agents

<table>
<thead>
<tr>
<th></th>
<th>Calcineurin inhibitors</th>
<th>Inosine monophosphate dehydrogenase (IMPDH) Inhibitors</th>
<th>Proliferation signal inhibitors</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis</td>
<td>Ciclosporin (Neoral)</td>
<td>Enteric-coated mycophenolate sodium (<em>myfortic</em>)</td>
<td>Everolimus (Certican)</td>
<td>Basiliximab (Simulect)</td>
</tr>
<tr>
<td>Astellas</td>
<td>Tacrolimus (Prograf)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche</td>
<td></td>
<td>Mycophenolate (Cellcept)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wyeth</td>
<td></td>
<td></td>
<td>Sirolimus (Rapamune)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Generic ciclosporin</td>
<td>Azathioprine (Imuran)</td>
<td></td>
<td>Thymoglobulin Anti-thymocyte globulin (ATGAM) OKT3</td>
</tr>
</tbody>
</table>

Structures of Small Molecule Immunosuppressive Drugs

- **CsA**
- **AZA**
- Tacrolimus (FK506)
- Sirolimus
- Prednisone
- Mycophenolic Acid Morpholinoethyl Ester (MMF)
Mechanisms of Action

- Signal 1: MHC/peptides recognition by TCR
- Signal 2: Costimulation
  - DC maturation
- Signal 3: IL-2R, IL-15, T-cell growth factors

- Resting DC
- MMF
- Steroids
- MMF
- Sirolimus

- T-Cell Activation
- T-Cell Proliferation

- Daclizumab
- Basiliximab
- CsA
- Tacrolimus
- Muromonab-CD3
- MMF
- Sirolimus

Adapted with permission from Professor Dr. Walter Land and M. Schneeberger, University of Munich, Germany.
Composite Downstream Effects of Immunosuppressants

Signal 3

- MMF
- Sirolimus, CsA
- Tacrolimus

Proliferation
- MMF
- Sirolimus, CsA
- Tacrolimus

Effector Function
- CsA
- Tacrolimus

Apoptosis
- MMF
- Sirolimus
# Downstream Effects

<table>
<thead>
<tr>
<th></th>
<th>CsA</th>
<th>Tacrolimus</th>
<th>MMF</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell proliferation</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>T-cell effector functions</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cytokine expression</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cytokine effects</td>
<td>-</td>
<td>-</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Apoptosis of activated T cells</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TGF-β induction</td>
<td>↑</td>
<td>↑</td>
<td>-</td>
<td>↑</td>
</tr>
</tbody>
</table>
ADULT HEART RECIPIENTS
Maintenance Immunosuppression at Time of Follow-up
((Follow-ups: January 2003 - June 2006

NOTE: Different patients are analyzed in Year 1 and Year 5

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ADULT HEART RECIPIENTS
Maintenance Immunosuppression at Time of 1 Year Follow-up

NOTE: Different patients are analyzed in each time frame.

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J Heart Lung Transplant 2007;26: 769-781
Why Poly-Drug Use

1) Side effects of one drug can be avoided / decreased!!

2) Drug-Combinations may have positive effects/Synergism
ADULT HEART RECIPIENTS
Maintenance Immunosuppression Drug Combinations at Time of Follow-up
For the Same Patients
((Follow-ups: January 1999 - June 2006

Year 1 (N = 4,447)  Year 5 (N = 4,447)

% of Patients

None
Other
Tacrolimus
Cyclosporine
Rapa + cellcycle
Rapa + calcineurin
Tacrolimus + MMF
Tacrolimus + AZA
Cyclosporine + MMF
Cyclosporine + AZA
ADULT HEART RECIPIENTS

Maintenance Immunosuppression Drug Combinations at Time of Follow-up

((Follow-ups: January 2004 - June 2006

NOTES: Different patients are analyzed in Year 1 and Year 5.

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Combinations of immunosuppressants

**DNA-synthesis inhibitors**
- Azathioprine or EC-MPS or MMF

**Calcineurin inhibitors**
- Ciclosporin or Tacrolimus

**Proliferation signal inhibitors**
- Everolimus or Sirolimus

**Corticosteroids**

**Polyclonal antibodies**
- ATG or ALG

**Monoclonal antibodies**
- OKT3 or Basiliximab or Daclizumab

**Combination possible:** Synergistically effective

**Combination possible:** Everolimus + CsA + corticosteroids (CsA dose reduction 1 month post-transplant); Sirolimus + CsA + corticosteroids (CsA withdrawal 3 months post-transplant)

Balance of Immunosuppression

Infections (viral)  Lymphomas (PTLD)

Acute Rejection chronic rejection (CAD, BOS)
<table>
<thead>
<tr>
<th>Major side effects</th>
<th>CsA</th>
<th>Tac</th>
<th>Aza</th>
<th>MMF</th>
<th>Rapa</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotocixity</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
<td>!!!</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>+++</td>
<td>+</td>
<td></td>
<td></td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Bone marrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>+++</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gingivahyperplasia</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>
Immunosuppressive Drug Toxicities

**CsA**
- Nephrotoxicity
- Neurotoxicity
- Hypertension
- Hyperlipidemia
- Hirsutism

**Steroids**
- Osteoporosis
- Weight gain
- Hyperglycemia
- Body changes
- Others

**Tacrolimus**
- Nephrotoxicity
- Neurotoxicity
- Hypertension
- Hyperglycemia
- GI toxicity

**MMF**
- Cytopenias
- GI toxicity

**Sirolimus**
- Hyperlipidemia
- Cytopenias
- GI toxicity
Safety of Immunosuppressants: Drug Interactions With CYP450

• Commonly encountered drugs that may affect CYP450
  – Azole antifungals: fluconazole, clotrimazole
  – Macrolide antibacterials: erythromycin, clarithromycin
  – Calcium channel blockers: nifedipine, verapamil
  – Anticonvulsants: phenobarbital, carbamazepine

## Interactions Between Immunosuppressants

<table>
<thead>
<tr>
<th>Interaction With</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA Sirolimus</td>
<td>Increased bioavailability</td>
</tr>
<tr>
<td>CsA MMF</td>
<td>Decreased MPA bioavailability</td>
</tr>
<tr>
<td>Tacrolimus MMF</td>
<td>Increased MPA bioavailability</td>
</tr>
<tr>
<td>Sirolimus MMF</td>
<td>?</td>
</tr>
<tr>
<td>Sirolimus Tacrolimus</td>
<td>?</td>
</tr>
</tbody>
</table>

## Immunosuppressive Management Vienna

<table>
<thead>
<tr>
<th></th>
<th>week 1</th>
<th>weeks 2-4</th>
<th>months 2-6</th>
<th>&gt;6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATG (Thymoglobuline)</strong></td>
<td>1-2.0mg/kg 3-7 days</td>
<td><strong>target level:</strong> 200-250 ng/ml</td>
<td><strong>target level:</strong> 150-200 ng/ml</td>
<td><strong>target level:</strong> 100-150 ng/ml</td>
</tr>
<tr>
<td><strong>Cyclosporine</strong></td>
<td>delay until days 2-7</td>
<td>delay until days 2-7</td>
<td>delay until days 2-7</td>
<td>delay until days 2-7</td>
</tr>
<tr>
<td><strong>Tacrolimus</strong></td>
<td>delay until days 2-7</td>
<td>target level: 12-15 ng/ml</td>
<td>target level: 10-15 ng/ml</td>
<td>target level: 5-10 ng/ml</td>
</tr>
<tr>
<td><strong>Mycophenolate-Mofetil</strong></td>
<td>2x500mg</td>
<td>2x1000mg</td>
<td><strong>EC-MPS</strong></td>
<td>2x720mg</td>
</tr>
<tr>
<td><strong>Everolimus 1.5mg/d</strong></td>
<td>start day 3</td>
<td>target level: 3-8 ng/ml</td>
<td>Sirolimus</td>
<td>target level: 5-10 ng/ml</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>500mg iv intra OP 3x125mg iv over first 24 h</td>
<td>0.2mg/kg/d</td>
<td>0.15-0.2mg/kg/d</td>
<td>0.1mg/kg/d</td>
</tr>
<tr>
<td></td>
<td>The pause until day 7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Utility of the Cylex Assay in Cardiac Transplant Recipients

Sachin Gupta, MD,a Joshua D. Mitchell, MD,b David W. Markham, MD,a Pradeep P. A. Mammen, MD,a Parag C. Patel, MD,a Patricia A. Kaiser, RN,c Peter Stastny, MD,d W. Steves Ring, MD,b J. Michael DiMaio, MD,b and Mark H. Drazner, MD, MSca

Background: Although the Cylex immune assay has been proposed as a means of tailoring immunosuppression after organ transplantation, there are limited data regarding its utility in cardiac transplant recipients. Therefore, we sought to determine the utility of the Cylex assay in assessing the risk of infection or rejection in cardiac transplant recipients.

Methods: This study is a retrospective review of the clinical course of all adult cardiac transplant recipients who underwent a Cylex assay at UT Southwestern Medical Center between January 2004 and September 2007.

Results: One hundred eleven patients were free of significant rejection or infection at the time of the first Cylex assay. Most patients (92%) were >1 year post-transplant. Over the next 157 ± 41 (mean ± SD) days, 2 patients had 3 episodes of rejection requiring therapy and 7 patients had 8 infections requiring therapy. The Cylex responses ranged from 17 to 894 ng/ml. No correlation was observed between the baseline Cylex response and subsequent risk of either infection or rejection within 6 months. Lower white blood cell count and African American ethnicity were correlated with a lower Cylex response.

Conclusions: In this study, the Cylex assay had limited utility as an adjunct to routine clinical evaluation in assessing risk of infection or rejection in cardiac transplant recipients. J Heart Lung Transplant 2008; 27:817–22. Copyright © 2008 by the International Society for Heart and Lung Transplantation.
MMF After Cardiac Transplantation

Study Design

• Twenty-eight centers in Australia, Europe, and North America
• Three year, double blind, active control
• Randomized prior to transplantation

Patients

• First cardiac transplant recipients enrolled between February 1994 and July 1995 (N = 650)
• Eleven percent of patients withdrew before receiving study drug
• Rejection and survival data obtained for 6 and 12 months, respectively

Immunosuppression

• MMF (n = 289) or AZA (n = 289)
• CsA and steroids
• ± antibody induction

MMF After Cardiac Transplantation

MMF-pivotal trial
Survival

Weighted pair wise diff 95% CI
6.548 (1.120 - 11.975)

AZA
81.6%

MMF
88.1%

p = 0.0294

Kobashigawa et al, TX 1998
Late Conversion From MMF to AZA After Cardiac Transplantation

Study Design
• Open-label, nonrandomized

Patients
• Stable heart transplant patients on long-term MMF therapy (N = 43)

Immunosuppression
• Patients continued on MMF therapy (n = 23)
• Patients were converted to AZA after an average of 41 months on MMF (n = 20)

Late Conversion From MMF to AZA After Cardiac Transplantation


Converted to AZA: Acute Rejection (%)

MMF Continued:

P = 0.002
Tacrolimus vs CsA in Cardiac Transplantation

Study Design

• Retrospective
• Joint ISHLT/UNOS Thoracic Registry data analyzed for effects of tacrolimus vs CsA in patients discharged on one of these two agents

Patients

• Cardiac transplant patients receiving CsA at time of discharge (n = 7,247 transplanted from 1994 to 1998)
• Cardiac transplant patients receiving tacrolimus at time of discharge (n = 396 transplanted from 1994 to 1998)

Tacrolimus vs CsA in Cardiac Transplantation

Patient Survival

<table>
<thead>
<tr>
<th>Percent</th>
<th>1 Year</th>
<th>3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>CsA</td>
<td>90%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Hosenpud JD, Bennett LE. *J Heart Lung Transplant.* 2001;20:161-162.
Tacrolimus/MMF vs CsA/MMF in Cardiac Transplantation

Patient Survival

Percent

• Superior prevention of acute rejection by TAC vs CSA in heart transplant recipients – a large European trial

During antibody induction, pts. were randomized (1:1)

TAC+AZA+ST  n=157 pt.

CSA+AZA+ST  n=157 pt.

Episodes of acute rejection were assessed by protocol biopsies

( Local and blinded central evaluation )
• Patient / graft survival (18 m) 92.9% 89.8% n=NS

• Incidence of first biopsy proven
  • Acute rejection grade =/ 1B (6 m) 54% 66.4% P=0.029

• Incidence of first biopsy proven
  • Acute rejection grade =/ 3A (6 m) 28% 42% P=0.013
TAC vs. CsA
Freedom from AR at Month 6

((EUROPEAN PHASE III STUDY

Generalized Wilcoxon test

Grimm et al. AJT 2006
<table>
<thead>
<tr>
<th>Condition</th>
<th>TAC</th>
<th>CSA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>New onset diabetes</td>
<td>20.3%</td>
<td>10.5%</td>
<td>0.05</td>
</tr>
<tr>
<td>Post Tx hypertension</td>
<td>65.6%</td>
<td>77.7%</td>
<td>0.05</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>28.7%</td>
<td>40.1%</td>
<td>0.05</td>
</tr>
<tr>
<td>(6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td>similar</td>
<td></td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td>similar</td>
<td></td>
</tr>
<tr>
<td>(18 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Arm Trial Tac-Srl/Tac-MMF/Csa-MMF 3
Probability of Rejection ≥ Grade 3A

Kobashigawa et al, AJT 2006
Tacrolimus or Cyclosporine: which is the better partner for MMF in heart transplant recipients?

Meiser BM et al.

Transplantation. 2004 Aug 27;78(4):591-8
SINGLE-CENTER STUDY

Randomized, prospective, open-label, controlled

60 PT.

MMF+TAC +ST  n=30

MMF+CSA +ST  n=30
Target blood trough levels

- TAC -10-15 ng/ml
- CSA -100-300 ng/ml
- MMF – 1.5-4.0 microg/ml
Baseline characteristics were well balanced

• All pt. were successfully withdrawn from corticosteroid within 6 months
Freedom from acute Rj. - significantly higher in TAC group (p=0.0001)

- Incidence of ARE per 100 pt. days
  - TAC+MMF 0.03
  - CSA+MMF 0.15

- P=0.00007
Overall pt. survival during follow-up was similar

93\% vs. 90\%

• To achieve the targeted MMF blood levels a significantly lower dose of MMF was required for TAC vs. CSA
• GRAFG VASCULAR DISEASE

• TAC+MMF  1.85 +/- 3.18
• CSA+MMF  3.95 +/- 4.8
• P=0.08
Influence of immunosuppression regimen on heart transplantation survival

• Aguero j et.al.

Comparing long –term survival in HT Pt depending on the immunosuppression regimen

• 317 consecutive HT pt.
• Excluded : pediatric cases
• Combined transplantation
• Retransplantation
• Immunosuppressive regimens with fewer than 10 y
The survival by groups at the end of follow-up:

- OKT3 7 days +CSA +MMF +ST      75.8%
- OKT3 7 days +CSA +AZA +ST       51.2%
- OKT3 10 days +CSA +MMF +ST      63.6%
- OKT3 10 days +CSA +AZA +ST      25.3%
- IL-2 antagonist +CSA +MMF +ST    91.2%
- IL-2 antagonist +TAC+MMF +ST     84.6%
Conclusions

• Association between the immunosuppressive regimen and long-term survival

• The best result were obtained with an induction based on IL-2 antagonist

• The maintenance combination we regard as “optimal” based on a combination of CSA, MMF and ST
RAD B253: Study Design

Randomization at first dose of Certican

Heart Transplantation

634 Patients
52 Centers

SAMPLE SIZE:

Primary efficacy failure: AZA 45%, Everolimus 30%
210 per treatment arm (two-sided alpha at 2.5%, power 80%)

*Study unblinded at 12 months

Baseline IVUS

6 month efficacy

12 & 24 month * safety/efficacy IVUS

4 year extension
Everolimus Pivotal Trial
Cumulative ISHLT AR Grade ≥ 3A – M 48

![Graph showing Kaplan-Meier estimates](image)

- AZA (n = 214) 49.1%
- Everolimus 1.5 mg (n = 209) 35.9%
- Everolimus 3.0 mg (n = 211) 24.2%

AZA vs everolimus 3 mg:
- *p ≤ 0.006

AZA vs everolimus 1.5 mg:
- +p = 0.005

RAD 1.5 mg vs everolimus 3 mg:
- **p < 0.001

RAD 3.0 mg vs everolimus 3 mg:
- **p < 0.001

Eisen et al, NEJM 2003
Everolimus

Why?

• Synergistic with CNIs (low rates of acute rejection)
• Non-nephrotoxic
• May be CNI and steroid-sparing
• Possibly anti-atherogenic
• Possibly anti-neoplastic

Why not?

• Synergistic with CNIs (enhanced nephrotoxicity)
• Side effects:
  – Hyperlipidemia
  – Bone marrow suppression
  – Impaired wound healing?
<table>
<thead>
<tr>
<th>Body system</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Viral, bacterial and fungal infections, sepsis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Leucopenia, thrombocytopenia, anaemia, coagulopathy</td>
</tr>
<tr>
<td>Metabolic and nutrition disorders</td>
<td>Hypercholesterolemia, hyperlipidemia, hypertriglyceridemia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Acne, surgical wound complication</td>
</tr>
</tbody>
</table>
Patient groups

**Pre-Transplant**
- Pediatrics
- Old patients (>60,65a)
- Diabetes
- Renal Insufficiency
- Pre-sensitized (PRA’s)
- Assist device
- Re-TX

**Post-Transplant**
- Rejection
- Infection (CMV)
- Diabetes
- Renal Insufficiency
- Hyperlipidemia
- Hypertension
- Vasculopathy
- Cancer
# Pediatrics vs. Old Patients

**Pediatrics**
- More rejections
- Growth
- Side effects
- Compliance
- Tac (no hirsutism)
- MMF
- Long term: use Rapa (low CNI or MMF)

**Old patients (>60-65)**
- Less rejections
- More Infections (CMV)
- Osteoporosis
- Diabetes
- Low CNI
- Lower MMF
- Long term: Rapa mono?

---

**Wean steroids!!**
New Era in Immunosuppression

IS scheme for all patients

Individualised Immunosuppression

PreTX rejection markers high (PRA’s, posXM)

Early rejection

- recurrent rejection
- Early development of graft vasculopathy or BOS

Late Retransplantation

- old Patients
- Diabetics
- Skin-tumors

Infections
- cancer
- Side effects

Combination of drugs depending on risk factors
Summary

• Immunosuppression gets more and more complicated
• Trials do not show everything
• IS-therapy will be dynamic not static
• Individualise according to patients needs
Guidelines for the future

• Never change a winning team

• If real problems occurs react quickly

• Life style changes can help too

• Play safe (if you switch)
Trouble makers

(Late Acute Rejection (LAR)
Late Rejection pitfalls/troubleshooting

- Reason #1: incompliance
- Reason #2: diarrhea (more than 3 days!!!)
- Mostly low Csa/Tac levels!
- Almost always hemodynamic compromise!!!
- Biopsy!
- Start therapy before diagnosis: 500mg Urbason
- After biopsy result > 0 two more doses!!
- heart failure therapy (inotropic support)
- Often vascular component--> ATG!!
Re-Transplantation

- Low number
- Chronic immunosuppression
- Lower risk for acute rejection?
- Higher risk for vasculopathy??
- Early CNI weaning (renal function side effects)
- Introduce rapa and/or MMF
Long-term Complications

**Vaculopathy**
- No influence of CNI
- Rapamycin (Srl/Evl) show better protection
- Therapy? (rapastat, Mancini)
- Steroid weaning?

**Cancer**
- Cumulative level of immunosuppression
- Aza potential cancerogen
- Less cancer with MMF
- Rapa possible antineoplastic
Effects of Sirolimus and MMF on Vascular Smooth Muscle Cell Proliferation and Migration

Sirolimus

FKBP12

Synergy

MMF

Proliferation

Migration

Contribution to Arteriopathy
TGF-β Mediates Important CsA Effects

- Blocks T-Cell Proliferation
- Promotes Fibroblast Proliferation (and Scarring)
- Promotes Angiogenesis

CsA

TGF-β

TGF-β Protein

T Cell

Endothelial Cell

Blood Vessel
PERCENTAGE OF ADULT HEART TRANSPLANT RECIPIENTS TREATED FOR REJECTION IN 1ST YEAR

(Stratified by Type of Induction  (Transplants: January 1, 2000 - June 30, 2005

Overall: no induct vs. OKT3 (p<0.0001); poly vs. OKT3 (p<0.0001); poly vs. IL2 (p=0.026); IL2 vs. OKT3 (p=0.013)
45-62: All comparisons with OKT3 (p=0.0005 or less).
No other comparisons within age groups were statistically significant at 0.05.
For females: no induction vs. OKT3 (p = 0.0006); polyclonal vs. OKT3 (p = 0.004); IL2R vs. OKT3 (p = 0.0157)
For males: no induction vs. OKT3 (p = 0.0038); polyclonal vs. OKT3 (p = 0.0386); IL2R vs. OKT3 (p = 0.002)

ISHLT 2007

J Heart Lung Transplant 2007;26: 769-781
NUMBER OF REJECTION EPISODES FOR ADULT HEART TRANSPLANT RECIPIENTS TREATED FOR REJECTION IN 1ST YEAR

(Transplants: January 1, 2000 - June 30, 2005)

Overall: no induction vs. OKT3 (p = 0.0017); polyclonal vs. OKT3 (p=0.0065); IL2 vs. OKT3 (p=0.0003).
18-44: no induction vs. IL2 (p = 0.037).
45-62: no induction vs. OKT3 (p = 0.0025); IL2 vs. OKT3 (p = 0.0034).
63+: polyclonal vs. OKT3 (p = 0.0228).

For females: no induction vs. OKT3 (p = 0.0078); IL2 vs. OKT3 (p = 0.0466).
For males: no induction vs. OKT3 (p =0.040); polyclonal vs. OKT3 (p=0.045); IL2 vs. OKT3 (p = 0.0022).

ISHLT 2007

J Heart Lung Transplant 2007;26: 769-781
• Randomized trial of TAC monotherapy: TAC in combination, compared to TAC alone (TICTAC Study)

• Baran DA JHLT 2007 (oct) ;26(10):992-7

• Prospective, Randomized, 2 center study

• April 2004 to Sept 2005

• TAC combination vs TAC monotherapy
• 58 pts.

• All received TAC +MMF +ST for 14 days

• MMF maintained vs. MMF discontinued

• (ST were rapidly withdrawn in both groups between 8-12 weeks)
Mean 6 month ISHLT biopsy score:

- Monotherapy: 0.44+/-.04
- Combined: 0.60+/-.05
- p=0.013

Freedom from rejection (2R or higher at 6,12 m):

- Monotherapy: 93.3%
- Combined: 92.9%
- P=NS
Conclusions:

- TAC monotherapy appears to be safe and efficacious in heart transplant recipients.

- It is not associated with excess rejection in the first year post transplantation.
Efficacy of Immunosuppressants in Cardiac Transplantation
Induction Therapy With Rabbit ATG After Cardiac Transplantation

Study Design
• Single center, European, retrospective

Patients
• Cardiac transplant recipients from March 1984 to December 1996 (N = 519)
• Five-year follow-up

Immunosuppression
• ATG-fresenius (n = 156) or thymoglobulin (n = 363)
• CsA, AZA, and steroids

Induction Therapy With Rabbit ATG After Cardiac Transplantation

Daclizumab for Cardiac Transplantation

Study Design
• Single center, randomized

Patients
• Nonsensitized cardiac transplant recipients from January to December 1998 (N = 55)
• Follow-up 502 ± 117 vs 454 ± 76 days for no daclizumab vs daclizumab groups
• January to December 1998

Immunosuppression
• Induction therapy with daclizumab (n = 28) for 3 months
• 1.0 mg/kg body weight IV within 24 hours posttransplantation and every two weeks thereafter (5 total doses) or no induction (n = 27)

Daclizumab for Cardiac Transplantation

Acute Rejection at 3 Months (%)

No Daclizumab

Daclizumab

$P = 0.04$

ADULT HEART RECIPIENTS
Maintenance Immunosuppression Drug Combinations at Time of Follow-up
((Follow-ups: January 2004 - June 2006

NOTES: Different patients are analyzed in Year 1 and Year 5. In the Year 1 cohort 73.9% of patients were on prednisone; in the Year 5 cohort 56.8% of patients were on prednisone.

ISHLT
J Heart Lung Transplant 2007;26: 769-781
## Safety of Immunosuppressants: Drug Interactions With CYP450

<table>
<thead>
<tr>
<th>Interaction With</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA</td>
<td>Increased bioavailability</td>
</tr>
<tr>
<td>P450 Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Increased bioavailability</td>
</tr>
<tr>
<td>P450 Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Decreased metabolism</td>
</tr>
<tr>
<td>(?)</td>
<td></td>
</tr>
</tbody>
</table>
