Transplantation in 2010: Good news, bad news, new news

Thomas C. Pearson, MD, DPhil

Emory Transplant Center
Emory University School of Medicine
Atlanta, USA
I have the following financial relationships to disclose:

- Research Grants: Roche, Bristol Myers Squibb

I will discuss the following off label use and/or investigational use of:

- cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, basiliximab, daclizumab, antithymocyte globulin, alemtuzumab, abatacept, belatacept
Transplantation in 2010: Good news, bad news, new news

- Current Status
- The Problem
- Improvements: Steps along the way
  Co-stimulation Blockade
  - islet cell transplantation
  - renal transplantation
- Tolerance
People Living with a Functioning Graft at Year End by Organ, 1999 - 2008

Number of Recipients

Year

Source: OPTN/SRTR Annual Report, Table 1.14
## Kidney Graft Survival Rates

<table>
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<tr>
<th>Condition</th>
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<tr>
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<td>78.1</td>
<td>66.1</td>
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Kaplan-Meier Analysis of 1997-2004  (Data as of 11/07/08)
**Patient Survival Rates**

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<td>83.0</td>
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Kaplan-Meier Analysis of 1997-2004 (Data as of 11/07/08)
USA National Transplant Waiting List
5/25/10

- TOTAL
- KIDNEY
- LIVER
- HEART
- LUNG
- KID/PANC
- PANCREAS

SRTR
Figure IV-13. Projected Growth in the Total and Active Waiting List for Deceased Donor Kidneys

## Kidney Median Wait Time

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<tr>
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<th>years</th>
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<td>B</td>
<td>1937</td>
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<td>AB</td>
<td>855</td>
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Patients listed 2003-2004  (Data as of 5/14/2010)
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- Current Status
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  - Co-stimulation Blockade
    - islet cell transplantation
    - renal transplantation
- Tolerance
Causes of Graft Loss

Causes of Graft Loss >6 Months
- Glomerulonephritis 6%
- Other 5%
- Chronic rejection 36%
- Death with function 50%

Causes of Death with Function
- Infection/sepsis 18%
- Cardiovascular 36%
- Unknown 17%
- Stroke 6%
- Malignancy 9%
- Accident/suicide 2%
- GI tract disorder 2%
- Other 10%

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>CI</th>
<th>P</th>
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<td>Recipient age (yr)</td>
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<td>Cause of ESRD (GN)</td>
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<td>ESRD time (preemptive)</td>
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<td>&lt;6 months</td>
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<td>Living donation</td>
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<td>0.92–0.98</td>
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<tr>
<td>Serum creatinine at 1 year (≤1.2)</td>
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<td>1.3–1.4</td>
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<td>1.5–1.6</td>
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<td>1.02–1.39</td>
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<tr>
<td>1.7–1.8</td>
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<tr>
<td>1.9–2.1</td>
<td>1.49</td>
<td>1.25–1.76</td>
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<tr>
<td>2.2–2.5</td>
<td>1.67</td>
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<td>2.6–4.0</td>
<td>2.26</td>
<td>1.85–2.75</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval.

Chronic Renal Failure after Transplantation of a Nonrenal Organ

Akinlolu O. Ojo, M.D., Ph.D., Philip J. Held, Ph.D., Friedrich K. Port, M.D., M.S., Robert A. Wolfe, Ph.D., Alan B. Leichtman, M.D., Eric W. Young, M.D., M.S., Julie Arndorfer, M.P.H., Laura Christensen, M.S., and Robert M. Merion, M.D.

Figure 1. Cumulative Incidence of Chronic Renal Failure among 69,321 Persons Who Received Nonrenal Organ Transplants in the United States between January 1, 1990, and December 31, 2000.

The risk of chronic renal failure was estimated with a noncompeting-risk model. Measurements of renal function were obtained at six-month intervals during the first year and annually thereafter.
Current Agents

- Calcineurin inhibitors
- Mycophenolate Mofetil
- Sirolimus
- Azathioprine
- Steroids
- IL-2R antagonists
- Anti-lymphocyte antibody preparations
- alemtuzumab
- Co-stimulation blockade
- Leflunomide
## Immunosuppression given in combinations

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<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
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<tr>
<td>Tacro</td>
<td>AZA</td>
<td>Pred</td>
</tr>
<tr>
<td>CsA</td>
<td>AZA</td>
<td>Pred</td>
</tr>
<tr>
<td>CsA</td>
<td>MMF</td>
<td>Pred</td>
</tr>
<tr>
<td>Tacro</td>
<td>MMF</td>
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<td>Tacro</td>
<td>Sirolimus</td>
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</tr>
<tr>
<td>CsA</td>
<td>Sirolimus</td>
<td>Pred</td>
</tr>
</tbody>
</table>
Immunosuppression given in combinations

- CSA
- CsA
- MMF
- Tacro
- Sirolimus

- AZA
- Pred
- Rapamycin

Can decrease dose of CNI
Can decrease dose of MMF/Sirolimus
Can give fixed dose
Can never use MMF/AZA or Sirolimus
Can dose on CNI levels
Can dose on levels
Can replace CNI with Rapamycin
Can dose on C-2 levels
Can stop calcinein inhibitors
Can never use steroids
Possible drug combinations: 168

Members of AST: 2000
Immunosuppression: Limitations

- inadequate efficacy
  - acute and chronic rejection
  - T1/2 - 14 yrs
- non-specific
  - infection
  - cancer
- Medication side effects
  - High blood pressure
  - Elevated cholesterol
  - Hirsuitism
  - Moon Facies
  - Gum hyperplasia
- Cost - $10,000-15,000/yr
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  Co-stimulation Blockade
  - islet cell transplantation
  - renal transplantation
- Tolerance
Immunosuppression: Goals 2010

- Maintain efficacy
  - acute rejection

- Improve toxicity profile
Background

- **Type 1 Diabetes Mellitus**
  - absence of insulin production
  - destruction of pancreatic beta cells
  - a multisystem disease
Multicenter, randomized clinical trial (n = 1441)
- Intensive therapy vs conventional therapy
- F/U 6.5yrs
- Results: intensive therapy effectively delays the onset and slows the progressions of retinopathy, neuropathy, and nephropathy
Problems with medical management

- The need to follow a meticulous diet, exercise regimen, frequent daily blood glucose measurements, and daily injections
- Increased risk of serious hypoglycemic events
- Healthcare cost

American Diabetes Association’s Clinical Practice Recommendations
- Pancreas transplant (SPK) is an acceptable procedure in type 1 diabetics undergoing renal transplant
- Pancreas transplant alone (PTA) should be considered in the setting of frequent, acute metabolic complications, incapacitating clinical or emotional problems with exogenous insulin

America Diabetes Association Pancreas Transplantation for patients with type 1 Diabetes. Diabetes Care 2004
Transplantation of the Pancreas

- Currently the “standard” surgical management for diabetes
- Tight, physiological control of blood glucose
- Abrogates hypoglycemic unawareness
How to improve

- Pure B cell replacement therapy
- Eliminate the potential complications related to the exocrine portion of the gland
- Transition from a major → minor operative intervention
Pancreatic Islet Transplantation

- Minimal invasive procedure
- Experimental Procedure – not FDA approved
- Indications
  - *brittle* diabetics
  - hypoglycemic episodes
From Pancreas to Islet Cells...
Modern Era of Pancreatic Islet Transplantation

Pancreatic Islet transplantation in the late 20th century (1990s)

- Significant improvements in islet isolation
  - Camillo Ricordi
- 267 transplants performed
  - 12.4% insulin independence longer than a week
  - **8.2% insulin independence > 1yr**
- Steroid-based immunosuppressive regimen
Modern Era of Pancreatic Islet Transplantation

Pancreatic Islet transplantation in the late 20\textsuperscript{th} century (1990s)

- Significant improvements in islet isolation
  - Camillo Ricordi
- 267 transplants performed
  - 12.4\% insulin independence longer than a week
  - \textbf{8.2\% insulin independence > 1yr}
- Steroid-based immunosuppressive regimen
• Balance between efficacy and toxicity of immunosuppressive agents
• 2 transplants required
• 11,547 IEQ/kg to establish insulin independence
Emory Experience: Pancreatic alloislet transplantation

8 recipients with debilitating hypoglycemia after failed intensive insulin therapy.
<table>
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<tr>
<th>Subject</th>
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<th>2</th>
<th>3</th>
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<td>250,681</td>
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<td>373,280</td>
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</tr>
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<td>36 mo</td>
<td>&lt;0.1</td>
<td>3 mo</td>
<td>&lt;0.1</td>
<td>6 mo</td>
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<tr>
<td>48 mo</td>
<td>&lt;0.1</td>
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<td>&lt;0.1</td>
<td>6 mo</td>
<td>&lt;0.1</td>
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<tr>
<td>72 mo</td>
<td>&lt;4.1</td>
<td>3 mo</td>
<td>&lt;0.1</td>
<td>6 mo</td>
<td>&lt;0.1</td>
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<tr>
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<th>Time Frame</th>
<th>C-Peptide After MMT*</th>
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<td>0.4</td>
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<tr>
<td>3 mo</td>
<td>0.4</td>
<td>3 mo</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>6 mo</td>
<td>2.8</td>
<td>3 mo</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>12 mo</td>
<td>3.1</td>
<td>3 mo</td>
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<tr>
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<td>3 mo</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>48 mo</td>
<td>3.1</td>
<td>3 mo</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>60 mo</td>
<td>3.1</td>
<td>3 mo</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>72 mo</td>
<td>3.1</td>
<td>3 mo</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complete Graft Function</th>
<th>Partial Graft Function</th>
<th>Graft Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Legend:
- **Complete Graft Function**
- **Partial Graft Function**
- **Graft Failure**
Five-Year Follow-Up After Clinical Islet Transplantation

Edmond A. Ryan,¹ Breay W. Paty,¹ Peter A. Senior,¹ David Bigam,² Eman Alfadhli,¹
Norman M. Kneteman,² Jonathan R.T. Lakey,² and A.M. James Shapiro²

DIABETES, VOL. 54, JULY 2005

~ 10% insulin independence

~ 85% graft function
Barriers to the widespread application of islet cell transplantation

• Insufficient islet mass
• Poor islet engraftment
• Inadequate immunosuppression: rejection of the islets
• Toxicity of the immunosuppressive agents to the islets
Transplantation in 2010: Good news, bad news, new news

- T cells play a central role in graft rejection
- Co-stimulation pathways critical for T cell function
Critical Costimulatory Pathways

B7-1 (CD80) - B7-2 (CD86) - CD28 - CTLA4

MHC - TCR

CD40 - CD154 - IL-12

- Enhanced T cell survival
  - NF-κB activation
  - Bcl-XL upregulation

- Enhanced bioenergetics

- IL-2 synthesis
Non-Human Primate Islet Transplantation Model

- Rhesus macaque 3-5 kg
- Pancreatectomy-induced diabetes
- MHC typed and mis-matched
- Single donor transplants
- >10,000 IE/kg

Andrew Adams
N. Kenyon Miami
Calcineurin Inhibitor–Free CD28 Blockade-Based Protocol Protects Allogeneic Islets in Nonhuman Primates

Andrew B. Adams,¹ Nozomu Shirasugi,¹ Megan M. Durham,¹ Elizabeth Strobert,² Dan Anderson,² Phyllis Rees,¹ Shannon Cowan,¹ Huaying Xu,¹ Yelena Blinder,¹ Michael Cheung,¹ Dianne Hollenbaugh,³ Norma S. Kenyon,⁴ Thomas C. Pearson,¹,² and Christian P. Larsen¹,²

LEA29Y/Rapa/Basiliximab
Costimulatory Pathways: Targets for Selective Immunosuppression

- APC
  - ICAM-1
  - B7-1/2
  - LFA-3
  - TCR
  - CD2
  - CD28

- T cell
  - LFA-1
  - mTOR
  - Calcineurin

- T cell activation

LFA-1 blockers
Efalizumab
A Novel Targeted T-Cell Modulator, Efalizumab, for Plaque Psoriasis

Mark Lebwohl, M.D., Stephen K. Tyring, M.D., Ph.D., Tiffani K. Hamilton, M.D., Darryl Toth, M.D., Scott Glazer, M.D., Naji H. Tawfik, M.D., Ph.D., Patricia Walicke, M.D., Ph.D., Wolfgang Dummer, M.D., Xiaolin Wang, Sc.D., Marvin R. Garovoy, M.D., and David Pariser, M.D., for the Efalizumab Study Group

Figure 2. Mean Improvements in the Psoriasis Area-and-Severity Index during the First-Treatment Period.

The psoriasis area-and-severity index, based on skin surface involvement and the severity of erythema, desquamation, and plaque induration, ranges from 0 to 72, with higher scores indicating more severe disease and a reduction in the scores indicating improvement.
A Phase II open label, single center feasibility study

5 recipients with failed intensive insulin therapy

daclizumab

tacrolimus

mycophenolate

Efalizumab

Time post transplant
<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>IEQ x 10^-3</td>
<td>541,139</td>
<td>653,028</td>
<td>669,949</td>
<td>457,793</td>
</tr>
<tr>
<td>Day 75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HB A1C (%)</td>
<td>6.3</td>
<td>5.7</td>
<td>5.9</td>
<td>6.7</td>
</tr>
<tr>
<td>4 Mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HB A1C (%)</td>
<td>6.6</td>
<td>4.4</td>
<td>6.0</td>
<td>5.8</td>
</tr>
<tr>
<td>6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HB A1C (%)</td>
<td>6.4</td>
<td>5.6</td>
<td>5.9</td>
<td>5.8</td>
</tr>
<tr>
<td>12 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HB A1C (%)</td>
<td>5.7</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HB A1C (%)</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HB A1C (%)</td>
<td>6.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>C-peptide</td>
<td>1.0</td>
<td>2.8</td>
<td>0.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Glucose 102</td>
<td>113</td>
<td>108</td>
<td>136</td>
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</tr>
<tr>
<td>C-Peptide</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>After Boost</td>
<td>3.4</td>
<td>8.3</td>
<td>2.7</td>
<td>2.6</td>
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<tr>
<td>Insulin</td>
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<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Januvia 100mg</td>
<td></td>
<td>Januvia 100mg</td>
<td>Januvia 100mg</td>
<td>Januvia 100mg</td>
</tr>
</tbody>
</table>
As of June 9, 2009, Raptiva® (efalizumab) is no longer available in the United States. On April 8, 2009, Genentech announced a phased voluntary withdrawal of the psoriasis drug Raptiva from the U.S. market. The company's decision was based on the association of Raptiva with an increased risk of progressive multifocal leukoencephalopathy (PML), a rare and usually fatal disease of the central nervous system.

**WARNING:**

**RISK OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)**

- Raptiva increases the risk for PML, a rapidly progressive viral infection of the central nervous system that has no known treatment and that leads to death or severe disability. The risk of PML may markedly increase with longer duration of Raptiva exposure. The time dependent threshold when the risk for PML increases is unknown (see **WARNINGS**).
  - Patients on Raptiva should be monitored frequently to ensure they are receiving significant clinical benefit, to ensure they understand the significance of the risk of PML, and for any sign or symptom that may be suggestive of PML (see **WARNINGS**).
  - Raptiva dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, brain magnetic resonance imaging (MRI) and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended (see **WARNINGS**).

**RISK OF SERIOUS INFECTIONS**

- Infections, including serious infections leading to hospitalizations or death, have been observed in patients treated with Raptiva (see **WARNINGS** and **ADVERSE REACTIONS**). These infections have included bacterial sepsis, viral meningitis, invasive fungal disease and other opportunistic infections. Patients should be educated about the symptoms of infection and be closely monitored for signs and symptoms of infection during and after treatment with Raptiva. If a patient develops a serious infection, Raptiva should be discontinued and appropriate therapy instituted.
<table>
<thead>
<tr>
<th>Subject</th>
<th>1 (RAB)</th>
<th>2 (BJH)</th>
<th>3 (J-T)</th>
<th>4 (R-B)</th>
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<tr>
<td>Transplant 1 IEQ x 10^{-3}</td>
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<td>669,949</td>
<td>457,793</td>
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<tr>
<td>Protocol</td>
<td>Efalizumab to Abatacept 02/20/2009 At 26 months</td>
<td>Efalizumab to Abatacept 02/16/2009 At 12.1 months</td>
<td>Efalizumab to Abatacept 02/27/2009 At 6 months</td>
<td>Efalizumab to Abatacept 02/23/2009 At 4 months</td>
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<td>Transplant 2 IEQ x 10^{-3}</td>
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<tr>
<td>Transplant 3 IEQ x 10^{-3}</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Day 75 post transplant HbA1C (%)</td>
<td></td>
<td></td>
<td></td>
<td>6.7</td>
</tr>
<tr>
<td>4 Months post transplant HbA1C (%)</td>
<td>6.6</td>
<td>4.4</td>
<td>6.0</td>
<td>5.8</td>
</tr>
<tr>
<td>6 months post transplant HbA1C (%)</td>
<td>6.4</td>
<td>5.6</td>
<td>5.9</td>
<td>5.8</td>
</tr>
<tr>
<td>12 months post transplant HbA1C (%)</td>
<td>5.7</td>
<td>5.3</td>
<td>7.0</td>
<td>6.3</td>
</tr>
<tr>
<td>18 months post transplant HbA1C (%)</td>
<td>6.0</td>
<td>7.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 months post transplant HbA1C (%)</td>
<td>6.4</td>
<td>7.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 months post transplant HbA1C (%)</td>
<td></td>
<td></td>
<td>Withdrawn with partial graft function</td>
<td></td>
</tr>
</tbody>
</table>

- Complete Graft Function
- Partial Graft Function
- Graft Failure

★ converted to abatacept
Transplantation in 2010: Good news, bad news, new news

- Current Status
- The Problem
- Improvements: Steps along the way
  - Co-stimulation Blockade
    - islet cell transplantation
    - renal transplantation
- Tolerance
CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7

By Peter S. Linsley, William Brady, Mark Urnes, Laura S. Grosmaire, Nitin K. Damle, and Jeffrey A. Ledbetter

From the Oncogen Division, Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121

- CTLA4-Ig Dimer
- Retains Fc binding
- Non-complement fixing
- Serum T1/2 ~2 wks
- Immunologic tool and therapeutic fusion protein
TRANSPLANTATION TOLERANCE INDUCED BY CTLA4-Ig

THOMAS C. PEARSON, DIANE Z. ALEXANDER, KEVIN J. WINN, PETER S. LINSLEY, ROBIN P. LOWRY, AND CHRISTIAN P. LARSEN

Departments of Surgery, Pathology, and Medicine, Emory University School of Medicine, Atlanta, Georgia 30322; and Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121

Graph showing percent survival over time (days) with CTLA4-Ig treatment.

CTLA4-Ig
Rhesus Renal Allograft Model

- Yerkes Primate Research Center
- Adolescent Rhesus macaques
- Bilateral nephrectomy
- Unrelated MHC mis-matched
Effect of CTLA4-Ig on renal allograft survival in Rhesus macaques: Disappointing

CTLA4-Ig (16 mg/kg) immediately delayed

Assess survival, Cr

No intervention for rejection

Survival (%)

Time (days)

Immediate

Delayed

Control

CTLA4-Ig
Treatment of Rheumatoid Arthritis by Selective Inhibition of T-Cell Activation with Fusion Protein CTLA4Ig

Joel M. Kremer, M.D., Rene Westhovens, M.D., Ph.D., Marc Leon, M.D., Eduardo Di Giorgio, M.D., Rieke Alten, M.D., Serge Steinfeld, M.D., Ph.D., Anthony Russell, M.D., Maxime Dougados, M.D., Paul Emery, M.D., F.R.C.P., Isaac F. Nuamah, Ph.D., G. Rhys Williams, Sc.D., Jean-Claude Becker, M.D., David T. Hagerty, M.D., and Larry W. Moreland, M.D.

- Effective for treatment of rheumatoid arthritis
  - T cell-mediated autoimmune disorder
- Large safety experience with long-term administration
Belatacept (LEA29Y): Engineered for more potent co-stimulation blockade

- Second generation CTLA4 derivative human IgG1 Fc fusion protein
- aa substitutions at position 29 and 106
  - 2-fold higher avidity to B7-1
  - 4-fold higher avidity to B7-2 than parent CTLA4-Ig molecule
  - 10-fold higher biologic potency in vitro

Extracellular portion of CTLA4 (CD152)

Larsen et al AJT 2005
Costimulation Blockade with Belatacept in Renal Transplantation

Flavio Vincenti, M.D., Christian Larsen, M.D., Ph.D., Antoine Durrbach, M.D., Ph.D., Thomas Wekerle, M.D., Björn Nashan, M.D., Ph.D., Gilles Blancho, M.D., Ph.D., Philippe Lang, M.D., Josep Grinyo, M.D., Philip F. Halloran, M.D., Ph.D., Kim Solez, M.D., David Hagerty, M.D., Elliott Levy, M.D., Wenjiong Zhou, Ph.D., Kannan Natarajan, Ph.D., and Bernard Charpentier, M.D., for the Belatacept Study Group∗

- **In comparison to cyclosporine (CsA) belatacept treated patients have:**
  - Comparable patient/graft survival and acute rejection rates
  - Favorable renal function, renal histology at 1 year ****
  - Comparable safety overall
  - Favorable CV/metabolic changes and CNI-related AEs
Phase III Belatacept vs Cyclosporine (CsA) in Kidney Transplantation

Belatacept, a first-in-class costimulation blocker that selectively inhibits T-cell activation, is designed to avoid nephrotoxicity and increased cardiovascular and metabolic risk associated with CNIs

**BENEFIT (IM103-008)**
- Adult recipients of living and standard criteria deceased kidney donors (SCD)

**BENEFIT-EXT (IM103-027)**
- Adult recipients of extended criteria kidney donors (ECD)
**BENEFIT Study Design**

**Randomization**

**Belatacept MI***
- n = 219
- 10 mg/kg
- 5 mg/kg every 4 weeks
- DAY 1 5 14 28 42 56 70 84 112 140 168

**Belatacept LI***
- n = 226
- 10 mg/kg
- 5 mg/kg every 4 weeks
- DAY 1 5 14 28 56 84 112

**Cyclosporine***
- n = 221
- 150–300 ng/ml
- 150–250 ng/ml
- DAY 1 28

**Primary clinical endpoints**
- 6 months
- 12 months
- 24 months
- 36 months

*All patients received basiliximab induction, mycophenolate mofetil, and corticosteroids

LI = less intensive; MI = more intensive.
BENEFIT Endpoints at 12 Months

Co-primary endpoints

◆ Subject and graft survival (non-inferiority)
◆ Composite renal impairment endpoint (superiority)
  – Iothalamate GFR < 60 mL/min/1.73 m²
  or
  – Decrease ≥ 10 mL/min/1.73 m² from Months 3–12
◆ Acute rejection (clinically-suspected and biopsy-proven)
  – Confirmed by central pathologist (blinded readings)

Secondary endpoints

◆ Mean iothalamate GFR at Month 12
◆ Mean calculated GFR at Month 12 (MDRD formula)
◆ Chronic allograft nephropathy (CAN; Banff 97)
◆ Hypertension
◆ Dyslipidemia
◆ New-onset diabetes after transplantation (NODAT)
Patients Surviving with Functioning Graft

Both belatacept groups met 10% NI margin
Incidences of graft loss and death similar among groups
Patients Meeting Composite Renal Impairment Endpoint

Composite renal function impairment = Month 12 mGFR < 60 mL/min or decreased mGFR from Month 3 – Month 12 ≥ 10 mL/min
Measured and Calculated GFR

<table>
<thead>
<tr>
<th>Measured and Calculated GFR</th>
<th>Iothalamate GFR (measured)</th>
<th>GFR MDRD formula (calculated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>LI</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>CsA</td>
<td>50</td>
<td>54</td>
</tr>
</tbody>
</table>

p < 0.0001
### Incidence of Acute Rejection Episodes

#### Banff grade, n (%)  

<table>
<thead>
<tr>
<th>Banff grade, n (%)</th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild acute (IA)</td>
<td>7 (3)</td>
<td>4 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Mild acute (IB)</td>
<td>3 (1)</td>
<td>8 (4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Moderate acute (IIA)</td>
<td>17 (8)</td>
<td>16 (7)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Moderate acute (IIB)</td>
<td>20 (9)</td>
<td>10 (4)</td>
<td>2 (1)</td>
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<tr>
<td>Severe acute (III)</td>
<td>2 (1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Did not meet 20% NI margin  
† Met 20% NI margin
Measured GFR With or Without Acute Rejection

Mean measured GFR (ml/min/1.73m²)

- **Belatacept MI**: 66.2 (n=149) vs. 61.8 (n=37)
- **Belatacept LI**: 65.1 (n=165) vs. 60.6 (n=25)
- **CsA**: 50.8 (n=171) vs. 48.3 (n=37)

Patients without AR

Patients with AR
CAN Prevalence

- **Belatacept MI (n = 219)**: 18 patients
- **Belatacept LI (n = 226)**: 24 patients
- **CsA (n = 219)**: 32 patients

Statistical significance:
- Belatacept MI vs. Belatacept LI: p = 0.0010
- Belatacept LI vs. CsA: p = 0.058
Cardiovascular/Metabolic Outcomes

- Systolic and diastolic blood pressure significantly lower in belatacept groups vs CsA (p < 0.05)
- Non-HDL cholesterol and triglycerides significantly lower in belatacept groups vs CsA (p < 0.05)
- Incidence of new-onset diabetes after transplantation (NODAT) trended lower in belatacept groups vs CsA (p = NS)

Additional detail to be presented: *Belatacept is Associated with Improved Cardiovascular and Metabolic Risk Factors Compared to Cyclosporine in Kidney Transplant Patients* (BENEFIT and BENEFIT-EXT Studies) by Vanrenterghem et al. Sunday, May 31, 2009, 5:30 pm. Exhibit Hall C
Conclusion

Belatacept immunosuppressive regimens better preserved kidney graft function/structure and improved the cardiovascular/metabolic risk profile compared to CsA
Transplantation in 2010: Good news, bad news, new news

- Current Status
- The Problem
- Improvements: Steps along the way
- Co-stimulation Blockade
  - islet cell transplantation
  - renal transplantation
- Tolerance
Transplantation in 2010: Good news, bad news, new news

- Tolerance
  - Long-term survival of allograft with normal function without the need for non-specific immunosuppression
  - Normal immune response to other foreign antigens.
The Nobel Prize in Physiology or Medicine 1960

"for discovery of acquired immunological tolerance"

Sir Peter Medawar
Therapeutic Chimerism and Tolerance: An elusive goal

Bone Marrow

Lethal Irradiation

Accepts donor allografts

Rejects third-party allografts


Immuno-ablation

myelo-ablation

Immunologic Tolerance to Renal Allografts after Bone Marrow Transplants from the Same Donors

Mohamed H. Sayegh, MD; Neil A. Fine, MD; John L. Smith, MD; Helmut G. Rennke, MD; Edgar L. Milford, MD; and Nicholas L. Tilney, MD

Therapeutic Chimerism and Tolerance:

Bone Marrow

Costimulation blockade - Immunomodulation
Busulfan - myeloconditioning
Transplantation in 2010: Good news, bad news, new news

- Tolerance
  - Possible in rodent models
  - Much more difficult in non-human primate models and in the clinic
    - Heterologous immunity
Emory Single Center Pilot Trial in Renal Transplantation

- Living donor renal transplant recipients
- Alemtuzumab induction
- sirolimus and belatacept chronic therapy
- Randomized to infusion of unfractionated donor bone marrow
- Systematically withdrawn from all chronic immunosuppressive therapy
Summary to Date

- Enrollment on target, 11 patients to date
- Well tolerated
- Steroid avoidance in 10/11 patients
- CNI avoidance in 11/11 patients
- Excellent renal function (improvement with time)
- Weaning process reached in first 2 patients
- Mechanistic studies prepared
A Day in the Life of a Transplant Recipient
Christian Larsen, MD, DPhil

Shannon Ritchie Cowan
David Gerber
Diane Alexander
Bunny (Rose) Hendrix
Toby Mathews
Farzad Nahai
Eric Elwwod
David O'Brien
Hong Rae Cho
Seung (Sunny) Ha-Waitaze
Mohamed Dyaa Saleen
Mary Williams
Joel Trambly
Adam Bingaman
Faraz Kerendi
Chris Roetenberg
Matthias Corbascio
Angello Lin
Carol Tucker-Burden
Joyce Tan
Mary O'Connell
Jongwon Ha
Matt Williams
Ajmal Hussain
Andrew Adams
Meghan Durum
Sung-Joo Kim
Nozomu Shirasu
Thomas Jones
Huaying Zhao
Michael Cheung
Nicolas Emmanouilidis
Phyllis Rees
Melody Walsh
Martin Kriegel
Betsy Holbrook
Jennifer Jiang
David Tong
Brent Koehn
Eun Lee
Leslie Kean
Mark Rigby
Kelly Hamby
Chris Gilson
Shivaprapaksh Gangappa
Keshana Borom
Maylene Wagener
Shana Coley
Mandy Ford
Hammeda Bello-Laborn
Alison Tretsky
Brad Harten
Zvonimir Milas
Ken Cardona
Bo Stapler
Pamela Lankford Turner
Taylor Deane
Kim Nguyen
Marti Russell
Christine Martens
Jose Cano
Justin Golub
Ken Newell
Ken Kokko
David Neujar
Ivana Ferrer
Erin Fears
Adriana Cardona
Timothy Weaver
Ali Charafeddine
Saranya Selveraj
Sharon Sen
Jose Avila
Aneesh Mehta
Robert Kampen
Bing Kampen
Hong Zhu
Brandi Johnson
Tamara Floyd
Katherine McMillan
Weston Miller
Alexa Turner
Alan Anderson
Virginia Oliva
Vanad Raofi
Sarah Syygert
Amino Mohamed
Ana Howells-Ferreira
Andrew Page
Avinash Agarwal
Linda Stemporta
Dana Duan
Brett Mendel
Caleb Wheeler
Chantrell Lowe
Cheryl Fields
Cindy Breeden
Dasia Webster
Erin Scott
Frank Leopardi
Frankie Crain
Jean Kwun
Jennifer Hutchinson
Jennifer Jackson
Johanna Moreno
Neal Iwakoshi
Churpose guo
Jun Wang
Yig Dong
Danya Liu
Beth Begley
Marti Sears
Mingqing Song
Natalie Reisman
Raul Badell
Rivka Elbein
Stephanie Monday
Sumeet Bahl
Susan Meed
Winxin Pang
Zain Ahmed
Jennifer Cheeseman
John Shires
Amy Lewis
Arash Grakoui
Karen Gorden
Lisa Carlson
Sean Caufiel
Linda Cendales
Regina Eady
Faith Burnett
Elizabeth Ferry
Cheryl Fields
Tamara Floyd
Desiree Hopson
Brandy Johnson
Ahn Kirk
Kenneth Kokko
Patti Long
Aron Lukacher
Robert Mittler
Johanna Moreno
Kenneth Newell
Susan Safley
Samantha Hanna
Stuart Knechtle
Nicole Turgeon
Vicky Webb
Gina White
Griselda McCorquodale
Karen Wyatt