Belatacept: A Revolution in Solid Organ Transplantation Or Simply a New Toy?

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Learning Objectives:
1. Describe the current challenges with immunosuppression in renal transplantation
2. Assess the benefits and risks of belatacept use in renal transplantation
3. Devise an evidence-based approach for use of belatacept in renal transplantation
BACKGROUND

I. Why is Belatacept Important?
   A. First biologic agent to be tested in fully powered phase III trials as primary maintenance immunosuppressant in solid organ transplantation
      i. Primarily studied in renal transplantation
   B. Potentially first new drug in more than 25 years to impact long-term allograft survival

II. Trends in Renal Transplantation
   A. Renal transplant is treatment of choice for end-stage renal disease1,2
      i. Increased patient survival, increased quality of life, and decreased costs vs. dialysis
   B. Organ demand vs. supply1,3,5
      i. Demand for donor organs far exceeds supply
         a. Currently, almost 86,000 patients are awaiting kidney transplantation in US3
         b. In 2008, 16,500 renal transplants occurred in US1
      ii. Efforts to increase organ availability1,4
          a. Improve organ donation awareness
          b. Increase living donation
          c. Establish criteria for increased cadaveric organ utilization [governed by United Network for Organ Sharing (UNOS)]
             1. Donation after cardiac death (DCD)4
             2. Expanded criteria donors (ECDs)1,5
                a) Includes donors who are ≥ 60 years old or donors 50-59 with two of the following: history of hypertension, death due to a cerebrovascular accident, or terminal Scr ≥ 1.5 mg/dL5
                b) May increase risk of delayed graft function, primary graft nonfunction, or shortened graft survival
   C. One-year rejection treatment rates
      i. Declined drastically over past decade from approximately 30% to 10%6
   D. Trends in allograft and patient survival7
      i. Increase in graft survival from late 1980s to mid 2000s
      ii. From 1997 to 2005, graft survival rates have remained steady

![Graft Survival Rates vs. Year of Transplant](image)

**Figure 1:** Unadjusted Graft Survival for Deceased-Donor, non-ECD Kidney Transplants7
III. Current Immunosuppression and Challenges in Transplantation

A. Current regimens
i. Most common maintenance regimen at time of renal transplant in US is tacrolimus + mycophenolate ± corticosteroids

B. Drug toxicity
i. Nephrotoxicity with calcineurin inhibitors (CNIs)\textsuperscript{1,8-11}
   a. Both tacrolimus and cyclosporine cause significant vasoconstriction of the afferent arteriole, leading to reduced renal blood flow and decreased glomerular filtration rate (GFR)
   b. Initially, may be reversible after discontinuation or improved with dose reduction of CNI
   c. Long-term effects may lead to irreversible chronic kidney disease
      1. Average decline in GFR is 1-2 mL/min/1.73m\textsuperscript{2} per year\textsuperscript{10}
      2. Chronic renal failure in non-renal transplantation is 16.5\%\textsuperscript{11}

ii. Metabolic and cardiovascular complications\textsuperscript{1,12-13}
   a. Common with CNIs, mTOR inhibitors, and corticosteroids
   b. New onset diabetes after transplant (NODAT) rates approximately 30\% within first two years of kidney transplantation\textsuperscript{12}
      1. Risk factors include obesity, family history of diabetes, African or Hispanic ancestry, hepatitis C, increased recipient age (>40 years), CNI use, and corticosteroid use\textsuperscript{1}
   c. Cardiovascular disease is leading cause of death in long-term transplant recipients\textsuperscript{13}

<table>
<thead>
<tr>
<th>Calcineurin Inhibitors (CNIs) (Cyclosporine and Tacrolimus)</th>
<th>mTOR Inhibitors (Sirolimus and Everolimus)</th>
<th>Corticosteroids (CS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose intolerance</td>
<td>Hyperlipidemia</td>
<td>Glucose intolerance</td>
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<tr>
<td>Hyperlipidemia</td>
<td>Hyperlipidemia</td>
<td>Hyperlipidemia</td>
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<td>Hypertension</td>
<td>Hypertriglyceridemia</td>
<td>Hypertension</td>
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<tr>
<td>Nephrotoxicity</td>
<td>Impaired wound healing</td>
<td>Peptic ulcers</td>
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<tr>
<td>Neurotoxicity</td>
<td></td>
<td>Weight gain</td>
</tr>
</tbody>
</table>

C. Over-immunosuppression
i. Infection\textsuperscript{16-17}
   a. ‘Net state of immunosuppression’ encompasses all factors which contribute to risk of infection, including dose, duration, and sequence of immunosuppressants
   b. Viral infections may have immunomodulatory effects
      1. Herpes viruses are most common
         a) Cytomegalovirus (CMV), Epstein Barr Virus (EBV), Herpes Simplex Virus (HSV), and Human Herpes Virus 8 (HHV-8)

ii. Malignancy\textsuperscript{18-20}
   a. Most common malignancies post-transplant
      1. Nonmelanoma skin cancers – occur in up to 82\% of transplant recipients\textsuperscript{19}
      2. Post transplant lymphoproliferative disorder (PTLD) – occurs in 1-11\% of all transplant recipients; reported in up to 2.3\% of renal transplant recipients\textsuperscript{19-20}
         a) Often associated with EBV, which infects B-cells
            i.) In a non-immunosuppressed individual, EBV-specific cytotoxic T-cells typically control EBV infected B-cells and prevent over-proliferation
            ii.) In a significantly immunosuppressed patient, T-cells can no longer control B-cells, which leads to over-proliferation of B-cells
b) Mortality 40-60%

c) Risk factors
i.) EBV mismatch: EBV-negative transplant recipient from EBV-positive donor
ii.) Lymphocyte-depleting therapy [e.g. rabbit anti-thymocyte globulin (rATG, Thymoglobulin®) and muromonab-CD3(OKT®3)]
iii.) Male gender
iv.) Transplant before the age of 18
v.) CMV disease or CMV mismatch

D. Renal graft complications
i. Delayed graft function (DGF)\textsuperscript{1,21}
   a. Defined as need for dialysis within 7 days from transplant
   b. Independent risk factor for acute rejection and impaired renal function within 1 year
   c. May reduce 1-year graft survival rates
   d. Risk increased with extended cold/warm ischemia times, ECDs, and DCDs

ii. Acute rejection (AR)\textsuperscript{1,22,24}
   a. Predominantly T-cell mediated, where T-cells infiltrate allograft
   b. Most cases occur within 3 months from transplant
   c. Previously thought to be ‘gold-standard’ to predict graft survival rates
   d. Impact of AR on graft survival
      1. Early (3-6 months) vs. late (>1 year) AR
         a) Risk for graft failure increases with later AR\textsuperscript{22}
      2. More severe AR increases risk of graft failure\textsuperscript{22}
      3. Return of renal function to baseline after AR
         a) Overall 6-year graft survival similar to patients without AR\textsuperscript{23}
      4. Number of AR episodes
         a) Improved survival with one vs. two or more AR episodes\textsuperscript{22}
   e. Tacrolimus vs. cyclosporine
      1. Reduced rates of AR with tacrolimus vs. cyclosporine, which may not affect patient or graft survival\textsuperscript{24}

iii. Renal function at one year post-transplant
   a. Correlates with long-term graft survival\textsuperscript{25}

iv. Interstitial fibrosis and tubular atrophy (IFTA)\textsuperscript{1}
   a. Often referred to as chronic rejection or chronic allograft nephropathy (CAN)
   b. Slow and indolent form of fibrosis and graft loss
   c. Causes
      1. CNI nephrotoxicity
      2. Viral infections
      3. Hypertension
      4. Slowly progressing immunologic activity
      5. Donor related factors
         a) Ischemia time
         b) Undetected kidney disease
      6. Recurrence of kidney disease in recipient
E. Economical impact
   i. Cost of immunosuppressants

<table>
<thead>
<tr>
<th>Table 2: Annual Costs for Renal Transplant Immunosuppressants (US 2008)</th>
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<tbody>
<tr>
<td>Brand tacrolimus (Prograf®)</td>
</tr>
<tr>
<td>Brand cyclosporine, microemulsion (Neoral®)</td>
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<tr>
<td>Generic cyclosporine, microemulsion</td>
</tr>
<tr>
<td>Brand mycophenolate mofetil (CellCept®)</td>
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<tr>
<td>Sirolimus (Rapamune®)</td>
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<td>Prednisone</td>
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   a. Significant cost of maintenance immunosuppressants may impact medication adherence
   b. Therapeutic drug monitoring (TDM)
      a. TDM is considered standard of care with CNIs and mTOR inhibitors
      b. Cost of TDM contributes to overall healthcare expense

IV. New Drug Development in Transplantation
A. New drug approvals by US Food and Drug Administration (FDA) are typically based on trials using noninferiority design
   i. Unethical to use placebo as comparator, when effective immunosuppressant combinations exist
   ii. Trials demonstrating superiority treatment regimens would require an unreasonably large number of patients
   iii. Belatacept trials followed this noninferiority approach
B. Noninferiority studies seeking FDA approval must be compared to FDA-approved regimens, which may not reflect common clinical practice
   i. Examples with belatacept trials
      a. Basiliximab was induction agent utilized, although rATG (Thymoglobulin®) is most common induction agent in practice
         1. rATG is only approved for treatment of acute rejection in renal transplant
      b. Cyclosporine + mycophenolate mofetil + corticosteroids was maintenance immunosuppressant regimen utilized, although tacrolimus + mycophenolate mofetil ± steroids is most common regimen in US
         1. Combination of tacrolimus and mycophenolate mofetil did not receive FDA approval in renal transplant until May 19, 2009
OVERVIEW OF BELATACEPT

V. Belatacept
   A. Novel biological immunosuppressant fusion protein
   B. First inhibitor of Signal 2 in T-cell activation for transplantation

VI. Review of T-Cell Activation\(^1\)
   A. Signal 1
      i. Antigen presenting cell (APC) displays antigen to T-cell via the major histocompatibility complex (MHC)
      ii. Antigen binds to T-cell receptor (TCR) causing an activation of the T-cell
      iii. Inevitably leads to increased production of interleukin-2 (IL-2)
   B. Signal 2
      i. APC binds to T-cell via CD80 (B7-1) and CD86 (B7-2) interaction with CD28
         a. Both CD80 and CD86 can bind with CD28 to regulate T-cell clonal expansion and differentiation
         b. When CD80 and CD86 bind with cytotoxic T-lymphocyte antigen-4 (CTLA-4), also known as CD152, T-cell activation and proliferation are inhibited, leading to anergy or apoptosis
            1. CTLA-4 is only expressed during T-cell activation
      ii. This process is referred to as costimulation and is required for T-cell proliferation
   C. Signal 3
      i. IL-2 binds to CD25 on T-cell
      ii. Results in stimulation of cell cycle leading to T-cell proliferation

![T-Cell Activation Pathway](image)

**Figure 2:** T-Cell Activation Pathway\(^3^4\)
VII. Belatacept Development and Mechanism of Action$^{1,35-36}$

A. In vitro models demonstrated T-cell anergy, or antigen-specific unresponsiveness, when signal 2 was blocked (no CD28 engagement)$^1$

B. Abatacept$^{35-36}$
   i. First recombinant immunoglobulin fusion protein, combining extracellular portion of CTLA-4 with constant-region fragment (Fc) of human IgG1
   ii. Provides selective costimulation blockade of T-cell activation
      a. Binds surface costimulatory ligands (CD80 and CD86) of APCs
         1. Interferes with interaction of CD80/86 and surface costimulatory receptor CD28 of T-cells (signal 2), which is required for T-cell activation
   iii. Approved for treatment of rheumatoid arthritis as Orencia$^{35}$
   iv. In rodent models, significantly prolonged transplanted organ survival time
   v. In non-human primate models, found to be ineffective at preventing transplanted solid organ transplant rejection

C. Belatacept (LEA29Y)$^{35-36}$
   i. Differs from abatacept by two amino acids, allowing for greater binding capacity
      a. 2 times the binding strength to CD80 and 4 times the binding strength to CD86 compared with abatacept$^{35}$
      b. Same mechanism of action as abatacept

   ![Figure 3: Development of Belatacept]$^{36}$

   ii. In non-human primate models found to effectively prolong renal allograft survival
      a. Mean renal allograft survival time with belatacept monotherapy was 45 days, compared to 8 days with abatacept$^{35}$
   iii. Also found to inhibit the production of anti-donor antibodies, which are believed to contribute to CAN/IFTA$^{35}$

VIII. Belatacept Pharmacokinetic Profile$^{37-39}$

A. Steady state volume of distribution: 10.6 L; 0.12 L/kg$^{37-38}$
B. Terminal half-life: 8-11 days$^{37-38}$
C. Belatacept clearance increased with baseline body weight, supporting weight-based dosing$^{38}$
D. Clearance unaffected by$^{38}$
   i. Age, gender, and race
   ii. Renal and hepatic function
   iii. Dialysis
E. Belatacept does not interact with mycophenolate, unlike cyclosporine which decreases exposure by ~40%.$^{1,39}$
CLINICAL TRIALS

IX. Belatacept Phase II Trial
A. One-year Phase II data


| Purpose | To assess efficacy and safety of a belatacept- vs. cyclosporine-based regimen in kidney transplant recipients |
| Design | Randomized, partially-blinded, parallel, active-controlled, multicenter (22 centers in US, Canada, and Europe) Phase II study between 2001-2003 |
| Enrollment |  |
| - Inclusion |  |
| - Adult recipients of renal allograft from non-HLA-identical living or deceased donor |
| - No more than 10% of included patients could have an increased risk for AR as determined by study investigators, including a panel of reactive antibodies (PRA) > 20% and previous renal transplant |
| - Exclusion |  |
| - Underlying renal disease which could recur, infection which would prevent transplant, history or evidence of cancer, positive crossmatch, history of drug or alcohol abuse or psychotic disorders, previous treatment with basiliximab, use of investigational drug within 30 days of transplant, and high risk kidney donors (donor age > 60 years/< 6 years, DCD, cold-ischemia time > 36 hours) |
| Methods |  |
| - Randomized to one of three treatment arms |
| - Belatacept Intensive |
| - 0-3 months: 10 mg/kg/dose on day 1, 5, 15, 29, 43, 57, 71, 85 |
| - 4-6 months: 10 mg/kg/dose on day 113, 141, 169 |
| - 7-12 months: 5 mg/kg every 4 or 8 weeks |
| - Belatacept Less Intensive (LI) |
| - 0-1 month: 10 mg/kg/dose on day 1, 15, 29 |
| - 2-3 months: 10 mg/kg/dose on day 57, 85 |
| - 4-12 months: 5 mg/kg every 4 or 8 weeks |
| - Cyclosporine (CsA), modified |
| - Initial dose: 4-10 mg/kg/day |
| - 0-1 month: Dose adjusted to trough CsA concentration of 150 – 400 ng/mL |
| - 2-12 months: Dose adjusted to trough CsA concentration of 150 – 300 ng/mL |
| - All patients received basiliximab (20 mg on day 0 and day 4), mycophenolate mofetil (MMF) 2 g/day, and corticosteroid taper |
| - Belatacept administered as 30 minute infusion |
| Outcomes |  |
| - Primary endpoint |
| - Clinically-suspected (rise in Scr > 0.5 mg/dL), biopsy-proven acute rejection (BPAR) at 6 months |
| - Secondary endpoints |
| - Measured GFR (iohexol clearance), hypertension, hyperlipidemia, incidence of BPAR or presumed AR, and overall safety |
| - Other analyses |
| - NODAT, rate of death and graft loss, calculated GFR, pharmacokinetics, and immunogenicity |
| - Post hoc: CAN incidence, treatment of hypertension |
| Statistics |  |
| - Intention to treat with all patients who underwent transplantation |
| - Primary endpoint was noninferior if upper bound of 95% confidence interval (CI) of difference < 20% |
| - Projected 70 patients per treatment arm would provide 85% power assuming a 15% rate of clinically-suspected, biopsy-proven AR and a 10% dropout rate |
| Results |  |
| - Enrolled 218 patients (Intensive = 74, LI = 71, CsA = 73) |
| - 164 patients completed 12 month phase (Intense = 58, LI = 55, CsA = 51; dropout rates = 22%, 23%, and 30%, respectively) |
| - Baseline donor and recipient characteristics similar |

<table>
<thead>
<tr>
<th>AR at 6 months</th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>CsA</th>
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</thead>
<tbody>
<tr>
<td>Difference from CsA</td>
<td>7%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.5%</td>
<td>-2.6%</td>
<td>-</td>
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<tr>
<td>-11.3, 8.3%</td>
<td>-12.3, 6.7%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Belatacept MI</td>
<td>Belatacept LI</td>
<td>CsA</td>
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<tr>
<td><strong>CNI at 12 months</strong></td>
<td>29%</td>
<td>20%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Difference from CsA</strong></td>
<td>-15.6%</td>
<td>-24.1%</td>
<td>-</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>-34.6%, 3.4%</td>
<td>-42.1%, 6.0%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Mean measured GFR at 12 months (n=96) in mL/min/1.73m²</strong></td>
<td>66.3 (p=0.01)</td>
<td>62.1 (p=0.04)</td>
<td>53.5</td>
</tr>
<tr>
<td><strong>Mean calculated GFR at 12 months (n=169) in mL/min/1.73m²</strong></td>
<td>72.4</td>
<td>73.2</td>
<td>68.0</td>
</tr>
<tr>
<td><strong>Graft loss (#) (all due to technical reasons)</strong></td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Patient death (#)</strong></td>
<td>1</td>
<td>0</td>
<td>4 (2 d/t CV reasons)</td>
</tr>
<tr>
<td><strong>Prevalence of hypertension</strong></td>
<td>22%</td>
<td>24%</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Hyperlipidemia requiring lipid-lowering medication</strong></td>
<td>36% (p=0.03)</td>
<td>32% (p=0.03)</td>
<td>-</td>
</tr>
<tr>
<td><strong>NODAT (%)</strong></td>
<td>12%</td>
<td>6%</td>
<td>12%</td>
</tr>
</tbody>
</table>

- AR endpoint: No AR occurred in any group after 6 months
- Safety
  - Adverse effects significantly higher in CsA vs. belatacept: Hypertrichosis and diabetes mellitus
  - Infection rates were similar among groups (73% belatacept groups vs. 75% CsA)
  - No infusion-related reactions occurred
  - Malignancy: 2 Intensive (1 breast, 1 PTLD), 0 LI, and 2 CsA (1 skin, 1 thyroid)
    - PTLD: 2 additional cases 2-13 months after intensive belatacept replaced by tacrolimus
      - Of the 3 cases, 2 had a primary EBV infection and the third received 10 days of muromonab-CD3 for AR

**Conclusions**
- At 6 months, belatacept was found to be non-inferior to CsA
- Both belatacept regimens demonstrated improved measured GFR vs. CsA
- Belatacept may have an improved cardiovascular/metabolic side effect profile
- Although not statistically significant, belatacept had lower rates of CAN
- 3 cases of PTLD were reported in Intensive belatacept regimen; all had risk factors (primary EBV infection and lymphocyte-depleting therapy)

**Strengths**
- Well-designed study
- Evaluated several parameters which will help determine when to utilize belatacept in transplantation
- Helped develop primary endpoints for Phase III trials

**Limitations**
- Utilized CsA as a comparator
- Wide non-inferiority range
- Partially blinded, which may have contributed to ~10% higher biopsy rate in belatacept
- DGF rates not reported; CAN reported, but post-hoc analysis
- Only designed to establish noninferiority of belatacept to CsA in regards to AR rates
- Limited number of patients had measured GFR (58.5% who completed 12 months)
- High dropout rate
- Infection prophylaxis protocol not established
- Overall, low AR rates

**B. Five-year Phase II extension data**

i. Of those in long-term extension, 78/102 patients in belatacept groups and 16/26 patients in CsA group completed 5 years of treatment

ii. Patients were self-selected population who did well during first 12 months

iii. Mean calculated GFR (mL/min/1.73m²)
  a. 12 months: 75.8 ± 20.1 with belatacept; 74.4 ± 22.7 with CsA
  b. 60 months: 77.2 ± 22.7 with belatacept; 59.3 ± 15.3 with CsA

iv. Deaths: 3 belatacept (2 with functioning graft, 1 with graft loss); 2 CsA (both with functioning graft)

v. Graft loss only: 1 belatacept, 0 CsA

vi. BPAR: 6 belatacept (4 on 8-week dosing and 2 on 4-week dosing), 0 CsA

vii. PTLD: 0 belatacept, 0 CsA
X. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) Phase III

A. One-year BENEFIT data

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To assess the efficacy of a belatacept-based regimen compared to a cyclosporine-based regimen in adult kidney transplant recipients receiving a living or standard criteria donor (SCD) organ at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Three year, randomized, parallel-group, active-controlled, multicenter (100 centers) Phase III study with enrollment beginning January 2006 and primary endpoints assessed June 2008</td>
</tr>
</tbody>
</table>
| Enrollment | • Inclusion  
  - ≥18 years of age; living or SCD kidney transplant with anticipated cold ischemia time of < 24h  
  - Exclusion  
  - ECD [Age ≥ 60 or ≥ 50 with 2 additional risk factors (cerebrovascular accident, hypertension, or serum creatinine > 1.5 mg/dL)] anticipated cold ischemia time of ≥ 24 hours, DCD, prior or concurrent non-renal solid organ transplant, and PRA ≥ 50% for first time transplants or PRA ≥ 30% in re-transplants |
| Methods | • Randomized to one of three treatment arms  
  - Belatacept More Intensive (MI)  
    - 0-3 months: 10 mg/kg/dose on day 1, day 5, and then week 2, 4, 6, 8, 10, & 12  
    - 4-6 months: 10 mg/kg/dose on week 16, 20, & 24  
    - 7-12 months: 5 mg/kg every 4 weeks  
  - Belatacept Less Intensive (LI)  
    - 0-1 month: 10 mg/kg/dose on day 1, day 5, and then week 2 & 4  
    - 2-3 months: 10 mg/kg/dose on week 8 & 12  
    - 3-12 months: 5 mg/kg every 4 weeks  
  - Cyclosporine (CsA)  
    - Initial dose: 4-10 mg/kg/day  
    - 0-1 month: Dose adjusted to trough CsA concentration of 150 – 300 ng/mL  
    - 2-12 months: Dose adjusted to trough CsA concentration of 100 – 250 ng/mL |
| Outcomes | • Coprimary endpoints  
  - Composite patient and graft survival  
  - Composite renal impairment  
    - Measured GFR < 60 mL/min/1.73m² at month 12 (iothalamate); OR  
    - Decrease in measured GFR ≥ 10 mL/min/1.73m² from month 3 to month 12  
  - Incidence of AR: Protocol-defined clinical suspicion and biopsy-proven  
    - Secondary endpoints at month 12  
    - Mean calculated GFR (MDRD) and measured GFR, CAN on protocol biopsy at week 52, mean systolic and diastolic blood pressure, NODAT, mean change in non-HDL cholesterol from baseline to month 12, and DGF |
| Statistics | • Intention to treat with randomized patients who received transplant  
  • Primary endpoint sequential testing procedure  
    1.) Patient and graft survival using 10% noninferiority  
    2.) Superiority of belatacept on renal function with a continuity-corrected chi-squared test  
    3.) AR using 20% noninferiority  
    • Two-sided alpha = 2.7% for each belatacept arm vs. CsA (to account for multiple comparisons), alpha = 5% overall for the entire study  
    • Measured GFR analyzed using ANOVA  
    • Projected 220 patients per treatment arm with 93% power that met all coprimary endpoints  
    • Absolute difference between belatacept and CsA could not exceed 3% for graft/patient survival |
| Results | • Randomized 666 patients (MI = 219, LI = 226, CsA = 221)  
  • 527 patients completed 12 month phase (MI = 173, LI = 181, CsA = 173; dropout rates = 21%, 20%, and 22%, respectively)  
  • Baseline donor and recipient characteristics similar |
Safety
- Acute infusion reactions occurred in 4 patients in each belatacept MI and LI groups
- Overall, infections were similar among groups; TB reported in 1 CsA patient
- Adverse reactions similar between groups except tremor (16% CsA vs. 4% MI, 5% LI)
- Malignancy: 5 MI, 4 LI, and 1 CsA
- PTLD

Conclusions
- At 12 months, belatacept provided similar efficacy to CsA and superior renal function
- Higher rates of malignancy, including PTLD, were observed with belatacept
- MI belatacept group did not meet AR noninferiority criteria, while LI belatacept group did
- AR episodes tended to occur within 3 months of transplantation
- Belatacept provided improved cardiovascular/metabolic adverse effect profile
- MI belatacept demonstrated significantly lower CAN; LI belatacept trended towards lower CAN

Strengths
- One of the largest prospective transplant studies conducted to date
- Evaluated several parameters which will help determine when to utilize belatacept in transplantation
- Measured GFR collected from 88% of patients
- Protocol biopsies at 12 months completed in 79% of patients

Limitations
- Utilized CsA as comparator
- CsA patients allowed lymphocyte-depleting therapy if DGF or renal impairment occurred
- Open-label for CsA vs. belatacept
- Bristol-Meyers Squibb sponsored study
- Only preliminary 1 year data
B. Two-year BENEFIT data (abstract)\textsuperscript{a0}


<table>
<thead>
<tr>
<th>Results</th>
<th>493/666 patients completed 2 years of treatment (MI = 164, LI = 176, CsA = 153)</th>
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<thead>
<tr>
<th></th>
<th>Belatacept MI (n=164)</th>
<th>Belatacept LI (n=176)</th>
<th>CsA (n=153)</th>
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<tbody>
<tr>
<td>Composite patient/graft survival</td>
<td>94%</td>
<td>95%</td>
<td>91%</td>
</tr>
<tr>
<td>Additional AR episodes from year 1 to 2</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Number of AR episodes occurring during 1\textsuperscript{st} year from BENEFIT</td>
<td>49 (22%)</td>
<td>39 (17%)</td>
<td>16 (7%)</td>
</tr>
</tbody>
</table>

- Renal endpoint:
  - Mean measured GFR for both belatacept MI and LI ~ 15-17 mL/min higher vs. CsA (p < 0.0001)
- CV/Metabolic endpoints:
  - Additional effects regarding lower LDL with both belatacept groups vs. CsA (p ≤ 0.002)
- Safety:
  - Overall safety results remained similar between groups
  - Malignancy and serious infection rates remained comparable between groups
  - PTLD occurred in two belatacept MI patients from year 1 to 2

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>At 24 months, belatacept continued to provide similar efficacy and superior renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No additional efficacy with MI vs. LI belatacept</td>
</tr>
<tr>
<td></td>
<td>Majority of AR with belatacept occurred early</td>
</tr>
<tr>
<td></td>
<td>Additional cases of PTLD occurred between year 1 and year 2</td>
</tr>
<tr>
<td></td>
<td>Belatacept demonstrated beneficial effects on LDL cholesterol</td>
</tr>
</tbody>
</table>
XI. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial from EXTended Criteria Donors (BENEFIT-EXT) Phase III

A. One-year BENEFIT-EXT data


| Purpose | To assess the efficacy and safety of a belatacept-based regimen compared to a cyclosporine-based regimen in adult kidney transplant recipients receiving an extended criteria donor organ at 12 months. |
|**Design** | Three year, randomized, parallel-group, active-controlled, multicenter (79 centers) Phase III study with enrollment beginning March 2005 |
|**Enrollment** | • Inclusion: At least 18 years of age and extended criteria donor (EXT) (Age ≥ 60 or ≥ 50 with 2 additional risk factors (cerebrovascular accident, hypertension, or serum creatinine > 1.5 mg/dL); anticipated cold ischemia time of ≥ 24 hours; or donation after cardiac death) |
|**Methods** | • Methods and randomization design identical to BENEFIT trial |

| Outcomes | • Coprimary endpoints*
  - Composite patient and graft survival
  - Composite renal impairment
    • Measured GFR < 60 mL/min/1.73m² at month 12 (iothalamate); OR
    • Decrease in measured GFR ≥ 10 mL/min/1.73m² from month 3 to month 12
  - Secondary endpoints at month 12
    • Mean measured and calculated GFR (MDRD), CAN on protocol biopsy at week 52, incidence of protocol defined clinically-suspected, biopsy-proven AR, mean systolic and diastolic blood pressure, NODAT, and change in serum cholesterol from baseline to month 12
  - AR endpoint: 81% of AR occurred within first 3 months |

| Statistics | • Intention to treat with randomized patients who received transplant
  • Primary endpoint sequential testing procedure
    - 1.) Patient and graft survival using 10% noninferiority
    - 2.) Superiority of belatacept on renal function using a continuity-corrected chi-squared test
  • Two-sided alpha = 2.7% for each belatacept arm vs. cyclosporine (to account for multiple comparisons), although alpha = 5% for overall study
  • Measured GFR analyzed using ANOVA
  • Projected 180 patients per arm with 80% power to meet all coprimary endpoints at the 0.05 significance level |

| Results | • Enrolled 543 patients (MI = 184, LI = 175, CsA = 184)
  • 387 patients completed 12 month phase (MI = 133, LI = 129, CsA = 125; dropout rates = 28%, 26%, 30%, respectively)
  • Baseline donor and recipient characteristics similar; major cause of donor mortality was CVA (69.8%) |

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>CsA</th>
</tr>
</thead>
</table>
| Composite patient/graft survival | 86% | 89% | 85%
| Difference from CsA | 1.6% | 3.8% | -
| 97.3% CI | -6.6%,9.9% | -4.3%,11.9% | -
| Composite renal impairment | 70.5% | 76.5% | 84.8%
| Difference from CsA | -14.4% | -8.4% | -
| 97.3% CI | -24.0%,4.7% | -17.8%,1.0% | -(p = 0.0018)
| Mean measured GFR (mL/min/1.73m²) | 52.1 | 49.5 | 45.2
| Difference from CsA | 6.9 | 4.3 | -
| 97.3% CI | 1.1,12.7 | -1.5,10.1 | -(p = 0.0083)
| AR incidence* | 17.9% | 17.7% | 14.1%
| Difference from CsA | 3.8% | 3.6% | -
| 97.3% CI | -4.7%,12.4% | -5.0%,12.3% | -

*Note: AR not primary endpoint in BENEFIT-EXT due to anticipated high rates of DGF*
Safety
- Acute infusion reactions occurred in 7 patients in MI group and 9 patients in LI group
- Overall, infections were similar among groups; except TB reported in 2 MI and 2 LI patients
- Adverse reactions similar between groups
- Malignancy: 4 MI (1 PTLD, 1 Kaposi’s sarcoma, 1 breast cancer, 1 colon cancer), 4 LI (2 PTLD, 1 myelodysplastic syndrome and 1 breast cancer), and 6 CsA developed malignancies (1 breast cancer, 1 renal neoplasm, 1 thyroid neoplasm, 1 transitional cell carcinoma, and 2 Kaposi’s sarcoma)

PTLD
- PTLD incidence and prevalence: 4/5 PTLD infections involved CNS
- 2/5 had CMV disease
- 3/5 had EBV negative serology pretransplant
- None had used lymphocyte-depleting therapy
- 3/5 died as of March 2009

Conclusions
- At 12 months, belatacept provided similar efficacy to cyclosporine and resulted in improved renal function in patients receiving an EXT kidney
- Higher rates of PTLD, specifically CNS PTLD, were observed in patients receiving belatacept
- The belatacept groups also appeared to have an improved cardiovascular/metabolic adverse effect profile compared with cyclosporine

Strengths
- Well-designed, large, multicenter trial
- Specifically analyzed EXT concerns, which included DCD donors and extended cold ischemia times
- Measured GFR
- Protocol biopsies at 12 months completed in 73% of patients
- Analyzed risk factors for developing PTLD

Limitations
- Utilized cyclosporine as a comparator
- Only preliminary 1 year data
- T-cell depleting therapy for DGF only permitted in CsA group (15% CsA group received)
- Open label for CsA vs. belatacept
- Sponsored by Bristol-Meyers Squibb

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DGF incidence</td>
<td>47%</td>
<td>47%</td>
<td>49%</td>
</tr>
<tr>
<td>CAN incidence</td>
<td>45%</td>
<td>46%</td>
<td>52%</td>
</tr>
<tr>
<td>Difference from CsA</td>
<td>-6.8%</td>
<td>-5.7%</td>
<td>-</td>
</tr>
<tr>
<td>97.3% CI</td>
<td>-18.2% to 4.7%</td>
<td>-17.2% to 6.0%</td>
<td>-</td>
</tr>
<tr>
<td>Increase from baseline in non-HDL (mg/dL)</td>
<td>12.6 (p = 0.002)</td>
<td>11.2 (p = 0.001)</td>
<td>29.3</td>
</tr>
<tr>
<td>Incidence of NODAT</td>
<td>2%</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Percent requiring ≥ 3 antihypertensive agents</td>
<td>39 - 43%</td>
<td>-</td>
<td>52%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DGF incidence</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CAN incidence</td>
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<td></td>
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<td>Difference from CsA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>97.3% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase from baseline in non-HDL (mg/dL)</td>
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<tr>
<td>Incidence of NODAT</td>
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<tr>
<td>Percent requiring ≥ 3 antihypertensive agents</td>
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</tr>
</tbody>
</table>

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- At 12 months, belatacept provided similar efficacy to cyclosporine and resulted in improved renal function in patients receiving an EXT kidney
- Higher rates of PTLD, specifically CNS PTLD, were observed in patients receiving belatacept
- The belatacept groups also appeared to have an improved cardiovascular/metabolic adverse effect profile compared with cyclosporine

Strengths
- Well-designed, large, multicenter trial
- Specifically analyzed EXT concerns, which included DCD donors and extended cold ischemia times
- Measured GFR
- Protocol biopsies at 12 months completed in 73% of patients
- Analyzed risk factors for developing PTLD

Limitations
- Utilized cyclosporine as a comparator
- Only preliminary 1 year data
- T-cell depleting therapy for DGF only permitted in CsA group (15% CsA group received)
- Open label for CsA vs. belatacept
- Sponsored by Bristol-Meyers Squibb
B. Two-year BENEFIT-EXT data (abstract)\textsuperscript{41}


**Results**
- 347 patients completed 2 years of treatment (MI = 116, LI = 119, CsA = 112)

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite patient/graft survival</td>
<td>83%</td>
<td>84%</td>
<td>83%</td>
</tr>
<tr>
<td>Mean measured GFR (mL/min/1.73m(^2))</td>
<td>52 (p = 0.028)</td>
<td>50 (p = 0.108)</td>
<td>45</td>
</tr>
<tr>
<td>Additional AR episodes from year 1 to 2</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Number of AR episodes occurring during 1(^{st}) year from BENEFIT</td>
<td>33 (18%)</td>
<td>31 (18%)</td>
<td>26 (14%)</td>
</tr>
</tbody>
</table>

- CV/Metabolic endpoints:
  - Benefits on lipids and blood pressure maintained
- Safety:
  - Overall safety results remained similar between groups
  - Malignancy and serious infection rates remained comparable between groups
  - PTLD occurred in one of each belatacept MI and LI groups from year 1 to 2

**Conclusions**
- At 24 months, belatacept continued to have benefit on renal function and cardiovascular endpoints, with comparable graft/patient survival vs. CsA
- No additional efficacy with MI vs. LI
- Additional cases of PTLD occurred between year 1 and year 2
- Minimal additional AR occurred

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XII. Pooled Safety Data of Belatacept Phase II and Phase III Trials\textsuperscript{42}

A. Analysis of data to July 2009 with median follow-up of approximately 2.4 years

**Table 3: Safety Profile of Belatacept from Phase II and III Studies\textsuperscript{42}**

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI (n = 477)</th>
<th>Belatacept LI (n = 472)</th>
<th>CsA (n = 476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of death (%)</td>
<td>83%</td>
<td>84%</td>
<td>83%</td>
</tr>
<tr>
<td>Serious adverse events (%)</td>
<td>71%</td>
<td>68%</td>
<td>69%</td>
</tr>
<tr>
<td>Overall malignancy (%)</td>
<td>10%</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Overall PTLD (#)*</td>
<td>8</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>CNS PTLD</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Serious infections (%)</td>
<td>37%</td>
<td>32%</td>
<td>36%</td>
</tr>
<tr>
<td>Polyoma (%)</td>
<td>7%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Fungal infections (%)</td>
<td>22%</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td>PML (#)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tuberculosis (#)</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*No cases of PTLD occurred after 18 months in belatacept groups
XIII. Belatacept EBV+, LI Subgroup Analysis

A. 85% of patients who were enrolled in the Phase II and Phase III belatacept trials were EBV+

<table>
<thead>
<tr>
<th>Figure 4: Benefit-Risk Profile of the Belatacept LI at 2 Years in EBV+ Kidney Transplant Recipients vs. CsA (CI 97.3% or 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. Outcome data includes only Phase III trials and safety data includes Phase II and III trials</td>
</tr>
<tr>
<td>ii. PTLD: 4 cases in EBV+, LI belatacept (2 renal, 2 CNS) vs. 0 in CsA EBV+ recipients</td>
</tr>
</tbody>
</table>

XIV. Summary of Phase II and Phase III Studies

A. Pros of belatacept
   i. No added benefit with MI vs. LI belatacept recipients
   ii. Improved renal function at least 2 years post-transplant with belatacept LI in SCD kidney transplants with increase in GFR of ~15 mL/min/1.73m² vs. CsA
      a. EXT kidney transplants had an increase in GFR of 5 mL/min/1.73m² with LI belatacept vs. CsA (not significant)
   iii. Improved patient/graft survival with EBV+ belatacept LI at 2 years vs. CsA in SCD recipients
   iv. Improved metabolic/cardiovascular profile with belatacept vs. CsA

B. Cons of belatacept
   i. Increased AR with belatacept EBV+, LI group in SCD kidney transplants
   ii. PTLD: 4 episodes in EBV+, LI belatacept group (1%) vs. 0 in EBV+ CsA group
   iii. PML: 1 case in MI belatacept group

XV. Other Active Phase II Studies Involving Belatacept

A. Switch from CNI in stable kidney transplant patients
B. Comparison of belatacept- with tacrolimus-based, steroid-avoiding regimens
C. Belatacept in liver transplant recipients vs. tacrolimus
STATUS AND SUMMARY

XVI. Status
A. FDA Approval27,48
   i. March 2010, FDA Cardiovascular and Renal Drugs Advisory Committee recommended FDA approval of belatacept for renal transplant recipients
   ii. May 2010, FDA reviewed two-year data from Phase III belatacept trials and requested an additional one year of data before approval in renal transplant
   iii. Manufacturer of belatacept, Bristol-Myers Squibb, intends to seek approval for LI regimen as indicated dosage in adult renal transplant recipients
      a. Will be contraindicated in EBV-negative or EBV-unknown patients
   iv. Timing of presentation of 3 year data to FDA unknown

XVII. Summary
A. Although 1-year graft survival rates in renal transplant exceed 90%, long term outcomes remain challenged with nephrotoxicity and metabolic/cardiovascular risks
B. New immunosuppressive agents must balance successful graft outcomes with overall costs and over-immunosuppression
C. Belatacept a novel biologic maintenance immunosuppressant which potentially may be FDA-approved in the following months

XVIII. Recommendations
A. Population for use
   i. EBV+ adult renal transplant recipients at low risk for acute rejection
   ii. Patients able to receive IV infusions every 4 weeks after the first 3 months of therapy
B. Population most likely to BENEFIT from belatacept
   i. Patients who are adherent with clinic visits, but may have adherence issues with taking medications (difficult to predict at time of transplant)
   ii. Patients at risk for developing metabolic/cardiovascular complications with CNIs
      a. Obese patients
      b. Hispanic ancestry
      c. Family history of diabetes
      d. Patient age > 40
      e. Previous cardiovascular event
C. Possible future niche populations in renal transplant
   i. Patients experiencing severe toxicity associated with CNIs, including nephrotoxicity and neurotoxicity
   ii. Patients with difficulty maintaining therapeutic drug levels with CNIs
D. Further precautions with use of belatacept
   i. Only use LI dosing regimen
   ii. Avoid in EBV-negative and EBV-unknown recipients
   iii. Avoid use in patients at high risk for AR
   iv. Avoid use of lymphocyte-depleting therapy if possible
   v. Avoid use in patients with PRA ≥ 50% for first time transplants or PRA ≥ 30% in re-transplants
   vi. Utilize appropriate antiviral prophylaxis49
References


Rostaing L, Nainan G, del C Rial M et al. Switch from a CNI- to a belatacept-based immunosuppressive regimen in kidney transplant recipients is safe and results in better renal function: 12 month results from a phase II study. *American Transplant Congress* 2010:abstract 166.


Appendix A

Abbreviations
APC: Antigen presenting cell
AR: Acute rejection
BENEFIT: Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial
BENEFIT-EXT: Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial – EXTended criteria Donors
BPAR: Biopsy-proven acute rejection
CAN: Chronic allograft nephropathy
CI: Confidence interval
CMV: Cytomegalovirus
CNI: Calcineurin inhibitor
CNS: Central nervous system
CsA: Cyclosporine
CTLA-4: Cytotoxic T-lymphocyte antigen-4
CV: Cardiovascular
DGF: Delayed graft function
EBV: Epstein-Barr virus
ECD: Expanded criteria donor
EXT: Extended criteria donor
FDA: Food and Drug Administration
GFR: Glomerular filtration rate
HDL: High-density lipoprotein
HHV-8: Human herpes virus 8
HLA: Human leukocyte antigen
HSV: Herpes simplex virus
IFTA: Interstitial fibrosis and tubular atrophy
IL-2: Interleukin 2
LEA29Y: Belatacept
LDL: Low-density lipoprotein
LI: Less intensive
MDRD: Modification of diet in renal disease
MI: More intensive
MMF: Mycophenolate mofetil
mTOR: Mammalian target of rapamycin
NODAT: New-onset diabetes after transplant
PCP: Pneumocystis jiroveci pneumonia
PML: Progressive multifocal leukoencephalopathy
PRA: Panel of reactive antibodies
PTLD: Post transplant lymphoproliferative disorder
SCD: Standard criteria donor
Scr: Serum creatinine
TDM: Therapeutic drug monitoring
TB: Tuberculosis
UNOS: United Network for Organ Sharing
VZV: Varicella zoster virus