Belatacept in Renal Transplantation

J. Harold Heldereman
Vanderbilt University School of Medicine
OBJECTIVES

1. Learn the immunologic basis for co-stimulatory blockade
2. Understand the rationale for belatacept
3. Review the outcome of Benefit at 2 and 5 years
4. Understand the advantages and disadvantages for Bela in kidney transplant
IMMUONOLOGIC RATIONALE
Three Signal Hypothesis
For Alloantigen Activation
Naïve T cell

Signal 1

Signal 2

IL-2R

Immune synapse

APC

CD40

MHC-antigen

B7

B7RP-1

Naïve T cell

TCR-CD3

CD40L

Signal 1

Signal 2

Signal 3

Activation

CD28

ICOS

IL-2

IL-2R

IL-2 mRNA
RATIONALE FOR USE OF BELATACEPT
CD 28 – CD 80/86 Pathway

1st studied reagent CTLA4-Ig
- fusion protein
- extra cellular domain of CTLA4
- Fc portion of human Ig

Excellent pre clinical results but less spectacular non-human primate data

Sayegh and Turkha NEJM 338:1998
CD28 – CD80/86

LEA 29Y (Belatacept)

- Leucine 104 → Glutamate
- Alanine 29 → Tyrosine

2nd generation CTLA4Ig

Substitutions increase theoretic efficacy

- 2 fold ↑ binding to CD 80
- 4 fold ↑ binding to CD 86
- 10 fold ↑ T cell function inhibition

Larsen et al AJT 5:2005
a. Large pool of effector T cells

High dose CTLA4-Ig

Tregs

Rejection

Tolerance

b. Small pool of effector T cells

High dose CTLA4-Ig

Tregs

Rejection

Tolerance
TWO AND FIVE YEAR RESULTS
OF BENEFIT TRIAL
A Phase III Study of Belatacept-based Immunosuppression Regimens versus Cyclosporine in Renal Transplant Recipients (BENEFIT Study)
Table 2: Outcomes: Patient/graft survival, renal function and structure and acute rejection

<table>
<thead>
<tr>
<th>Patient/graft survival</th>
<th>Belatacept MI (n = 219)</th>
<th>Belatacept LI (n = 226)</th>
<th>Cyclosporine (n = 221)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month 12 endpoints</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Patients surviving with functioning graft, n (%)</td>
<td>209 (95)</td>
<td>218 (97)</td>
<td>206 (93)</td>
</tr>
<tr>
<td>95% CI</td>
<td>92.7–98.2</td>
<td>94.1–98.9</td>
<td>88.9–96.5</td>
</tr>
<tr>
<td>Difference from CsA (97.3% CI)</td>
<td>2.2 (−2.9, 7.5)</td>
<td>3.2 (−1.5, 8.4)</td>
<td>–</td>
</tr>
<tr>
<td>Graft loss or death, n (%)</td>
<td>10 (5)</td>
<td>8 (4)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Graft loss</td>
<td>4 (2)</td>
<td>5 (2)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (3)</td>
<td>4 (2)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Death with functioning graft</td>
<td>6 (3)</td>
<td>3 (1)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Imputed as graft loss or death, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal function and structure</th>
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</thead>
<tbody>
<tr>
<td>mGFR &lt;60 mL/min/1.73 m² or decrease</td>
<td>115 (55)</td>
<td>116 (54)</td>
<td>166 (78)</td>
</tr>
<tr>
<td>Month 3–12 ≥10 mL/min/1.73 m², n (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>48.3–61.8</td>
<td>47.5–60.9</td>
<td>72.4–83.5</td>
</tr>
<tr>
<td>Difference from CsA (97.3% CI)</td>
<td>−22.9 (−32.6, −12.9)</td>
<td>−23.7 (−33.3, −13.7)</td>
<td>–</td>
</tr>
<tr>
<td>p-Value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>–</td>
</tr>
<tr>
<td>Mean mGFR, mL/min/1.73 m² (SD)</td>
<td>65.0 (30.0)</td>
<td>63.4 (27.7)</td>
<td>50.4 (18.7)</td>
</tr>
<tr>
<td>Estimated difference from CsA (97.3% CI)</td>
<td>14.6 (8.8, 20.3)</td>
<td>12.9 (7.2, 18.6)</td>
<td>–</td>
</tr>
<tr>
<td>p-Value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>–</td>
</tr>
<tr>
<td>CAN, n (%) [95% CI]</td>
<td>40 (18 [13.1–23.4])</td>
<td>54 (24 [18.3–29.5])</td>
<td>71 (32 [26.2–38.6])</td>
</tr>
<tr>
<td>Difference from CsA (97.3% CI)</td>
<td>−14.2 (−23.2, −5.0)</td>
<td>−8.5 (−17.9, 0.9)</td>
<td>–</td>
</tr>
<tr>
<td>Mild CAN (stage I), n (%)</td>
<td>21 (10)</td>
<td>29 (13)</td>
<td>41 (19)</td>
</tr>
<tr>
<td>Moderate CAN (stage II), n (%)</td>
<td>5 (2)</td>
<td>6 (3)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Severe CAN (stage III), n (%)</td>
<td>4 (2)</td>
<td>6 (3)</td>
<td>6 (3)</td>
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<table>
<thead>
<tr>
<th>Acute rejection</th>
<th></th>
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<tbody>
<tr>
<td>Acute rejection, n (%)</td>
<td>49 (22)</td>
<td>39 (17)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>16.9–27.9</td>
<td>12.3–22.2</td>
<td>3.8–10.7</td>
</tr>
<tr>
<td>Difference from CsA (97.3% CI)</td>
<td>15.1 (7.9, 22.7)</td>
<td>10.0 (3.3, 17.1)</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Banff grade, n (%)</th>
<th></th>
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</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 (IA)</td>
<td>17 (8)</td>
<td>16 (7)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Moderate acute (IB)</td>
<td>20 (9)</td>
<td>10 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Severe acute (III)</td>
<td>2 (1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>
CONCLUSIONS BENEFIT TRIAL

1. BELA AFFORDS EQUAL GRAFT AND PATIENT SURVIVAL AS CNI

1. THERE ARE MORE ACUTE EARLY REJECTIONS THAN CNI EASILY REVERSED

3. RENAL FUNCTION SUPERIOR TO CNI
Belatacept-Treated Patients Had Better Graft Survival at 7-Years Post-Transplant Compared With Cyclosporine-Treated Patients: Final Results From BENEFIT

F Vincenti¹, JM Grinyó², L Rostaing³, KM Rice⁴, SM Steinberg⁵, MC Moal⁶, M Polinsky⁷, U Meier-Kriesche⁷, CP Larsen⁸

¹University of California, San Francisco, CA, USA; ²University Hospital Bellvitge, Barcelona, Spain; ³University Hospital, and INSERM U563, IFR-BMT, Toulouse, France; ⁴Baylor University Medical Center, Dallas, TX, USA; ⁵Sharp Memorial Hospital, San Diego, CA, USA; ⁶Hôpital de La Cavale Blanche, Brest, France; ⁷BMS, Lawrenceville, NJ, USA; ⁸Emory University Transplant Center, Atlanta, GA, USA
Background

- Long-term allograft survival has not improved appreciably in kidney transplant recipients.
- No prospective phase III studies have examined patient outcomes beyond 5 years.
- In no prospective, phase III study has an immunosuppressive regimen demonstrated a survival advantage over CsA-containing regimens.
- Analyses of the phase III BENEFIT study at 3 and 5 years demonstrated that belatacept-based immunosuppression was associated with significantly better renal function vs. CsA in kidney transplant recipients.


CsA=cyclosporine A.

Objective

- Report the long-term efficacy and safety outcomes up to Year 7 (Month 84) in the ITT population of BENEFIT

ITT=intent-to-treat.
Study Design and Dosing

Transplantation

Day 1

Clinical endpoints (months)

Primary\(^a\)
12 24 36 84

Belatacept MI\(^b\)

10 mg/kg

DAY 1 5 14 28 42 56 70 84 112 140 168

\[\rightarrow 5 \text{ mg/kg every 4 weeks}\]

Belatacept LI\(^b\)

Approved regimen

10 mg/kg

DAY 1 5 14 28 42 56 84

\[\rightarrow 5 \text{ mg/kg every 4 weeks}\]

CsA\(^b\)

(7 ± 3 mg/kg daily)

150–300 ng/mL

DAY 1 28

\[\rightarrow 100–250 \text{ ng/mL}\]

Placebo infusions

\(^a\)Belatacept arms unblinded at 12 months.

\(^b\)All patients received basiliximab induction, mycophenolate mofetil, and corticosteroid taper.

CsA = cyclosporine A; LI = less intensive; MI = more intensive.
Mean follow-up: 70 mos (bela MI, 71.1 mos; bela LI, 72.0 mos; CsA, 66.3 mos)

Enrolled, n=738

Randomized, n=666

Belatacept MI
Randomized and transplanted, n=219

Randomized, transplanted, and treated, n=219

Discontinued, n=91
Ineligible for/refused entry to LTE, n=39
Withdrawal of consent, n=14
Adverse event, n=13
Death, n=13
Other, n=5
Lost to follow-up, n=4
Pregnancy, n=2
Poor/noncompliance, n=1
Lack of efficacy, n=0
Administrative reason, n=0

Completed 84 months, n=128

Evaluable at 84 months, n=153

Belatacept LI
Randomized and transplanted, n=226

Randomized, transplanted, and treated, n=226

Discontinued, n=90
Ineligible for/refused entry to LTE, n=34
Withdrawal of consent, n=20
Adverse event, n=11
Death, n=11
Lost to follow-up, n=4
Other, n=4
Lack of efficacy, n=3
Poor/noncompliance, n=1
Pregnancy, n=1
Administrative reason, n=1

Completed 84 months, n=136

Evaluable at 84 months, n=163

CsA
Randomized and transplanted, n=221

Randomized, transplanted, and treated, n=215

Discontinued, n=123
Ineligible for/refused entry to LTE, n=41
Withdrawal of consent, n=22
Death, n=23
Adverse event, n=12
Lost to follow-up, n=8
Lack of efficacy, n=6
Other, n=6
Poor/noncompliance, n=4
Administrative reason, n=1

Completed 84 months, n=92

Evaluable at 84 months, n=131
Kaplan–Meier Curves for Patient and Graft Survival.

Time to Death or Graft Loss From Randomization to Month 84

Survival Rate

Months

N at risk
Bela MI 219 212 208 206 204 202 199 153 151 149 146 142 135 131
Bela LI 226 220 218 216 213 209 204 165 161 159 152 151 142 130
CsA 221 208 206 202 199 197 186 137 123 117 112 107 102 100

Month 60
Month 84
Calculated GFR Over 84 Months*: Without Imputation

Mean cGFR (mL/min/1.73 m²) at Month 84:
- MI: 74.0
- LI: 77.9
- CsA: 50.7

Differences in calculated GFR were significantly in favor of each belatacept regimen vs. CsA at every time point (P<0.0001)
## Safety Summary Up to Month 84

<table>
<thead>
<tr>
<th></th>
<th>Belatacept MI (N=219)</th>
<th>Belatacept LI (N=226)</th>
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</thead>
<tbody>
<tr>
<td>Serious adverse events, n (%)</td>
<td>155 (70.8)</td>
<td>155 (68.6)</td>
<td>160 (70.2)</td>
</tr>
<tr>
<td>Incidence rate†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious infections – total‡</td>
<td>10.6</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Incidence rate†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any fungal infection*</td>
<td>7.8</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Any viral infection – total*</td>
<td>16.2</td>
<td>14.2</td>
<td></td>
</tr>
<tr>
<td>BK polyomavirus</td>
<td>1.2</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>2.3</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>1.9</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Any malignancy‡</td>
<td>2.1</td>
<td>1.8</td>
<td></td>
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</tbody>
</table>
### Patients With PTLD Up to Month 84 by EBV Status

#### EBV-positive patients

<table>
<thead>
<tr>
<th>Time Interval, months</th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>Cs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (incidence rate)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–12</td>
<td>0</td>
<td>2 (1.00)</td>
<td>0</td>
</tr>
<tr>
<td>12–24</td>
<td>1 (0.54)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24–60</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60–72</td>
<td>0</td>
<td>0</td>
<td>1 (1.00)</td>
</tr>
<tr>
<td>72–84</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overall</td>
<td>1 (0.09)</td>
<td>2 (0.18)</td>
<td>1 (0.01)</td>
</tr>
</tbody>
</table>

#### EBV-negative patients

<table>
<thead>
<tr>
<th>Time Interval, months</th>
<th>Belatacept MI</th>
<th>Belatacept LI</th>
<th>Cs (incidence rate)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12</td>
<td>1 (4.29)</td>
<td>0</td>
<td>1 (2.07)</td>
</tr>
<tr>
<td>12–24</td>
<td>1 (4.49)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Incidence rates are calculated based on the total number of cases observed in each time interval.
In the 7 year study de novo donor specific antibody Formation was reduced compared to CNI group

Summary

- In this analysis of the final 7 year results from BENEFIT, belatacept-treated patients had better graft survival and renal function than CsA-treated patients.

- The belatacept safety profile was consistent with previous reports.
ADVANTAGES

1. ADHERENCE
2. NO NEED FOR ORAL ABSORPTION
3. NO NEPHROTOXICITY
4. NO CONCERNS ABOUT GENETIC DIFFERENCES IN METABOLISM
DISADVANTAGES

1. CAN ONLY BE USED IN EBV POSITIVE
2. REQUIRES iv ADMINISTRATION
3. MORE EARLY CELLULAR REJECTION
4. MORE EXPENSIVE