Costimulation blockade for prevention of acute GVHD

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Lack of costimulation leads to tolerance

APC

MHC Ag TCR

CD80/86 CD28

T cell → Activation

APC

MHC Ag TCR

CD80/86 CTLA4 CD28

T cell → Lack of costimulation, suppression
Rationale for consideration of costimulation blockade as part of GVHD Prophylaxis

- Blockade of the required “second signal” may prevent alloreactive donor T cell activation and clonal expansion
  - Effect may be additive with conventional immunosuppressive approaches
  - Possibility of induction of donor-host tolerance
  - Theoretically should be less suppressive of protective immune reconstitution and GVL effects

Abatacept--CTLA4 Ig

![Diagram showing the interaction between APC, T cell, MHC, Ag, TCR, CD80/86, CD28, and CTLA4 Ig](Image)

- APC presents MHC Ag to T cell
- Costimulation through CD80/86 and CD28
  - Activation of T cell
- Blockade of CTLA4 Ig
  - Lack of costimulation, suppression
Costimulation blockade in renal transplantation

• Goals
  • Eliminate the need for long term CNI use
  • Promote long term graft tolerance that might permit d/c of all immune suppression

• BENEFIT and BENEFIT-EXT studies
  • Multicenter RCTs comparing 2 non-CNI Belatacept containing regimens with a standard CSA-based regimens for prevention of rejection
  • Similar rates of pt and graft survival
  • Early T cell mediated rejection was more common in Belatacept-treated arms, but was generally treatable
  • Belatacept arms had better renal function and markers of CV risk
  • Belatacept arms had higher incidence of PTLD (still only ~1% @ 1 yr)
  • No difference in clinically significant infections


CD28/B7 Costimulation Blockade

Slow translation into the HSCT setting

• Abatacept: FDA approved for RA
• Belatacept: FDA approved for prevention of rejection post renal transplantation

• Mixed results in preclinical models of HSCT
  – Human CTLA4 not fully cross reactive with canine and rodent targets
  – Redundancy in mechanisms producing the second signal
Abatacept Prevents GVHD in Both Murine and Non-Human Primate Models

In Vivo Blockade of CD28/CTLA4: B7/B7.1 Interaction With CTLA4-Ig Reduces Lethal Murine Graft-Versus-Host Disease Across the Major Histocompatibility Complex Barrier in Mice

By Brian R. Hwang, Patricia A. Taylor, Peter S. Linney, and Daniel A. Valera

Miller and Kean, 2010

Pilot study of costimulation blockade for prevention of GVHD

• Single arm, single center pilot study of Abatacept (CTLA4Ig) added to CSP + MTX for GVHD prophylaxis

• Conditioning with Bu-CY, TBI (12Gy) - CY, or Flu-Mel

• Endpoints
  – Safety
  – PK/PD
  – Incidence and severity of aGVHD and cGVHD
  – Opportunistic infections
  – Immune reconstitution

Koura et al. BBMT 2013, 19: 1638-49
Inclusions

- Patients (adults and children) with hematologic malignancies receiving an allogeneic transplant from an **unrelated donor**
  - Preference for patients with a one locus mismatched donor
- Normal renal, hepatic and cardiac function
- No active infection or other active malignancy
- No concurrent participation in other therapeutic trials for which GVHD or infection was a primary endpoint

Abatacept Pilot Study

- **Conditioning**: -1, +6, +14, +28, +42, +100, +180, +365
- **Abatacept**
- **Cyclosporine + MTX (days +1, 3, 6, 11)**

**Correlative studies**: Aba PK, qualitative immune reconstitution, EBV and CMV-specific T cell recovery, cytokine profiles
Patient Population
n=10

<table>
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<th>UPN</th>
<th>Age, y/oex</th>
<th>Disease and Status</th>
<th>HLA Matching (Mismatch)</th>
<th>CMV Status (R/LD)</th>
<th>Preparative Regimen</th>
<th>Graft Source</th>
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<td>PBGS</td>
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<td>BM</td>
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<td>7/8 (DRB1 antigen)</td>
<td>+/-</td>
<td>TBI/Cy</td>
<td>BM</td>
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</table>

Engraftment and early toxicities

- All patients engrafted
  - Median time to neutrophil engraftment- 17 d (11-47)

- Full donor chimerism in T cell and myeloid compartments

- Abatacept delivered safely--no infusional events

- No unanticipated early toxicities or events
Viral infections

• CMV
  – 5 of 8 pts at risk reactivated CMV
  – No CMV disease
• EBV
  – 1 pt - low level reactivation (PCR)
  – 1 pt - EBV related plasmacytic hyperplasia (PCR neg)—resolved without therapy
• BK virus HC: 1 pt
• Adenoviremia: none
• No life-threatening viral infections

GVHD, relapse, and survival

• Acute GVHD
  – Gr 2: 2 pts (one late aGVHD during CSA withdrawal)
  – Gr 3: 1 pt (gut)
• Chronic GVHD
  – Mild-2, moderate-3, severe-2
  – Two cGVHD-related deaths
• Deaths
  – Relapse has occurred in 2 pts (both with MRD prior to HPCT), and both pts died on days +121 and +147
  – Two late non-relapse deaths with ongoing cGVHD
Overall Survival

6 of 10 pts remain alive in continuous remission at a median of 3.5 yrs post-transplant

Abatacept Pharmacokinetics in HSCT

Abatacept Concentrations (mcg/mL)

Average Trough

Average Peak

Terminal Half Life

Healthy Control (n=13) | RA (n=14) | HPCT (n=10)
Reconstitution of CD4+ and CD8+ T cells

**Day 100 CD4+ T cell Counts**

- + Abatacept
- *Historical Controls

*Historical Controls:
43 patients transplanted at EUH between 2007-2011 who met eligibility criteria for Aba trial

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**A shift toward T cell effector memory**

**CD4+ T Subsets**

- CD4+TNaive
- CD4+TCM
- CD4+TEM
- CD4+TEMRA

**CD8+ T Subsets**

- CD8+TNaive
- CD8+TCM
- CD8+TEM
- CD8+TEMRA
Treg recovery overlaps with untreated controls

Reduced proliferation of CD4+ T cells at early time points
The ability of CD8 effector cells to respond appropriately to CMV is preserved

Conclusions

- Murine and non-human primate studies laid the foundation for a ‘first-in disease’ trial investigating CD28-directed costimulation blockade with Abatacept for GvHD prevention.
- Feasibility established in this trial.
- First demonstration of the pharmacokinetic and pharmacodynamic impact of abatacept in HSCT patients.
- Encouragingly low rates of early severe GvHD.
- At day 100, CD4+ and CD8+ T cell reconstitution is similar to patients not treated with abatacept.
- Viral disease has not been a major clinical problem.
- These results have led to the design of a randomized, double-blind, placebo controlled multi-center phase 2 trial.
Phase 2 Trial: Abatacept combined with CNI + MTX for GVHD prophylaxis

- **Design:** Phase II multicenter, randomized, double blind, placebo controlled trial

- **Primary Objective**
  - To determine if the addition of costimulation blockade to standard GVHD prophylaxis can reduce the incidence of grade II-IV aGVHD in pts receiving URD transplants for hematologic malignancies

- **Secondary Objective**
  - To characterize the impact of Abatacept on post-transplant reconstitution of protective antiviral immunity

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Phase II Study Design

- **Eligibility**
  - >5 yrs old
  - High-risk leukemia
  - Lack of an HLA matched related donor
  - Availability of a volunteer donor matched at 7/8 or 8/8 HLA loci by high resolution allele level typing

- **Conditioning:** Bu/Cy, TBI/Cy, Flu/Mel, Bu/Flu

- **Two Strata**
  - 8/8 match: Randomization (n=75)
    - CNI + MTX + Aba/placebo (blinded)
  - 7/8 match: all pts will receive CNI + MTX + Aba (n=35)
    - Comparison with a case-control CIBMTR cohort (n=70)
Safety

• Stopping rules
  – **Day 100 transplant-related mortality:** The trial may continue as long as the hypothesis that 100-day TRM is less than or equal to 20% is not rejected
  – **PTLD:** The development of malignant PTLD will be monitored in the 2 arms, and the trial may continue as long as the hypothesis that the incidence of malignant PTLD is less than or equal to 5% is not rejected

Correlative Biology

• PK and pharmacodynamic analysis
• Immune reconstitution of T, B, NK subsets
• Quantitative and qualitative analysis of T cell activation and regulation
• Quantitative analysis of CMV-specific, EBV-specific, and BK-specific CD8+ T cells
• Functional analysis of anti-CMV, EBV, and BK immunity
• PCR-based monitoring for viral replication
• Serum cytokine and chemokine analysis
Implementation

- NIH funding and IND in place (PI: L. Kean)
- Bristol-Meyers Sqibb providing study drug
- PBMTC is coordinating the study
- Biorepository receiving samples
- Open sites
  - Emory, CHOA, FHCRC, Florida, Cincinnati, Michigan, Utah, Wash U, DC Children’s, Hackensack
- **Accrual to date: 29 subjects**
- DSMB monitoring ongoing

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**PBMTC PROTOCOL GVH 1201: Abatacept Combined with a Calcineurin Inhibitor and Methotrexate for Graft Versus Host Disease Prophylaxis: A Randomized Controlled Trial**

FDA IND#: 111738  SPONSOR: Leslie S. Kean, M.D., PhD  
PRODUCT NAME(S): CTLA4lg, abatacept, Orencia

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Thanks!