Co-stimulatory **B**lockade to **R**educe **A**ntibodies Following **H**eart **T**ransplantation
(**CoBRA HT** Pilot Protocol)

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Background
Although heart transplantation (HTx) remains the "gold standard" for the treatment of end-stage heart disease, outcomes remain suboptimal in patients developing de novo donor-specific antibodies (dnDSA)[1]. Indeed, persistent dnDSA develop in 25 - 30% of HTx recipients[2-5] and are associated with a 4-fold higher risk of death[1]. Recent studies have identified a number of risk factors for dnDSA and treated AMR, including black race[3] and the use of a bridge-to-transplant LVAD strategy[4, 6].

Given the suboptimal outcomes associated with dnDSA, there remains a critical need to develop novel pharmacological strategies to prevent their development. Recent evidence from the renal transplant literature has shown marked reduction in the formation of post-transplant dnDSA with immunosuppressive regimens incorporating belatacept, a co-stimulatory blocker[7]. Despite the successful use of belatacept in kidney transplantation, the drug has not been used in HTx recipients.

Purpose: Utilize co-stimulatory blockade with belatacept *early after transplant* (with tacrolimus) and as *standard of care* in heart transplant recipients to reduce the risk of developing dnDSA and mitigate the risk of common medical co-morbidities that result from long-term calcineurin inhibitor exposure.

Population
The protocol will be utilized as standard of care for all heart transplant recipients meeting the inclusion/exclusion criteria:

1. Belatacept criteria for use:
- a. EBV positive serology (**positive viral capsid antigen IgG**)

2. Exclusion criteria:
- a. EBV negative (**negative viral capsid antigen IgG**)
- b. High risk for CMV (R-/D+)
- c. HIV+
- d. **ANY** History of PTLD, lymphoma or hematologic malignancy

Note: EBV seropositive patients are defined as having evidence of acquired immunity shown by the presence of IgG antibodies to viral capsid antigen (VCA). IgM antibodies to viral capsid antigen or IgG antibodies to EBV nuclear antigen (EBNA) may be positive or negative.

3. Other patient considerations
- a. Transportation/Location
- b. Difficult intravenous access

CoBRA B (belatacept) PROTOCOL:

The heart transplant program's primary immunosuppression protocol will include basiliximab induction and maintenance therapy with belatacept plus tacrolimus overlap, mycophenolate mofetil and corticosteroids. Patients who do not meet criteria to receive belatacept maintenance long-term will receive basiliximab along with tacrolimus, mycophenolate mofetil and corticosteroids.

CoBRA B protocol: BELATACEPT (with tacrolimus overlap)

1. Basiliximab and corticosteroids will be given intra-op.

	Intra-op	POD1	POD2	POD3	POD4
Basiliximab	20mg IV	x	x	x	20mg IV
Tacrolimus	Per surgeon				
MMF	Per surgeon				
Corticosteroids	Per surgeon				

1. Belatacept Schedule

a. First dose will be given 3 months after transplant with eligibility based on most recent EBV test results documented in the patient's EeMR
- Each case will be discussed in multidisciplinary meeting prior to initiation

b. Subsequent maintenance doses will be given on a MONTHLY schedule
c. 5mg/kg – beginning 90 days post transplant and monthly thereafter
d. Window is +/- 5 days for all doses
e. Coordinate infusions and MD visits to minimize patient travel
f. Current expectation – patient will come to EUH for all infusions for the first 12 months
g. If patient gets off schedule, maintain original belatacept schedule for next dose

2. Belatacept Dosing

a. Available as lyophilized powder 250mg vial size
b. Rounding doses to minimize waste and reduce errors as follows:

5 mg/kg dose based on last recorded weight (mg)	Rounded dose (mg)
< 282.4999	250
282.4999 – 337.4999	325
337.5 – 422.4999	375
422.5 – 564.4999	500
564.5 – 674.4999	625
674.5 – 844.4999	750

c. For belatacept given at EUH, dose will be automatically calculated based on current weight
d. For patients receiving belatacept outside of EUH, a standard dose will be determined at the time of transition. Dose will be reassessed annually.

3. Belatacept Administration

a. Over 30 minutes via peripheral IV through a low protein binding filter (pore size of .2-1.2 um)
b. Admixed doses may be stored refrigerated for up to 24 hours protected from light
c. Cannot be infused with other agents – no data available
d. All patients should be asked for any signs and symptoms of infection. Pre-infusion checklist to be documented prior to every infusion. Screening form and pre-infusion checklist in eEMR under adhoc charting, located in transplant folder
e. CBC and BMP to be drawn prior to each belatacept infusion [but may infuse before lab results are available]
f. Notify MD prior to infusion for temp > 38

ADDITIONAL CONSIDERATIONS:

Tacrolimus dosing and schedule

a. Tacrolimus goal trough levels:
   a. 8-12 ng/ml ≤ 3 months
   a. 5-8 ng/ml for >3-6 months post-transplant
   b. 3-5 ng/ml for months 6-18 post-transplant if 6 month biopsy is ok
   c. TAC continuation and/or goal trough to be determined after 18 months

Additional Considerations

a. Patients should be maintained on mycophenolate mofetil at doses of 1000 mg BID or greater whenever possible, barring adverse side effects

b. The decision to completely wean off of tacrolimus after 18 months will be at the discretion of the transplant leadership team and with the use of Immuknow assays checked with each biopsy

c. The decision to reduce belatacept dosing frequency to q2months will be at the discretion of the transplant leadership team

d. Evaluation for DSA will occur q6 months in years 2 and 3 post-transplant

e. All patients at intermediate risk for CMV (R+) will receive CMV prophylaxis for 3 months starting at day 21 post- transplant with valganciclovir as is current practice.
   - CMV PCR's will be checked monthly for at least the first 6 months post-transplant

f. All patients at low risk for CMV (R-/D-) will receive prophylaxis with valacyclovir starting at post-op day 21 for 3 months as is current practice.

g. In Quantiferon + patients, start INH at time of transplant or if feasible, start treatment prior to transplant.

Endpoints to be specifically evaluated:

a. dnDSA development at 6, 12, 18, and 24 months
b. Freedom from treated ACR (2R+) at 6, 12, 18, and 24 months
c. eGFR at 6, 12, 18, and 24 months
d. Graft dysfunction as 6, 12, 18, and 24 months
e. Patient survival at 6, 12, 18, and 24 months
f. Treated HTN at 6, 12, 18, and 24 months (number of agents, doses)
g. Treated DM at 6, 12, 18, and 24 months (oral agents, insulin, doses, A1c)
h. Lipid profile at 6, 12, 18, and 24 months
i. Infectious complications (CMV PCR+, CMV admission, CMV organ involvement; EBV PCR or infection; admission for additional infectious complication.

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