Renal Allograft Tolerance Through Mixed Chimerism

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Synopsis

Title	Renal Allograft Tolerance Through Mixed Chimerism
Short Title	Renal Allograft Tolerance
Trial Phase	Phase I
Conducted by	MGH, Transplant Surgery
Principal Investigators	A. Benedict Cosimi, M.D. Tatsuo Kawai, M.D., Ph.D. Nina Tolkoff-Rubin, M.D.
Accrual Objective	5 participants with end-stage renal disease (ESRD) and no evidence of prior sensitization, and their donors
Study Design	Pilot study
Pace of Enrollment and Study Duration	Enrollment will be limited to one patient every three months

Participants will be followed for a total of 3-4 years after combined bone marrow and kidney transplantation (24 months after withdrawal of immunusuppression). Assessments will be performed for participant and graft survival, and long term adverse events.

Endpoint	**The primary endpoint** is Induction of transient mixed chimerism and renal allograft tolerance (24 consecutive months off of immunosuppression)

Recipient Inclusion Criteria

1. Male or female 18–60 years of age.

2. Candidate for a living-donor renal allograft from an HLA mismatched donor

3. First or second transplant with either a living donor or cadaveric transplant as the first transplant.

4. Use of FDA-approved methods of contraception (those with less than a 3% failure rate) by all recipients from the time that study treatment begins until 104 weeks (24 months) after renal transplantation. (For further information on FDA- approved methods of contraception, see http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118465.htm

5. Ability to understand and provide informed consent.

6. Serologic evidence of prior exposure to EBV.

Recipient Exclusion Criteria

1. ABO blood group-incompatible renal allograft.

2. Evidence of anti-HLA antibody within 60 days prior to transplant as assessed by routine methodology (AHG and/or ELISA)

3. Leukopenia (WBC less than 2,000/mm3) or thrombocytopenia.

4. Seropositivity for HIV-1, hepatitis B core antigen, or hepatitis C virus (confirmed by hepatitis C virus RNA); or positivity for hepatitis B surface antigen.

5. Cardiac ejection fraction < 40% or clinical evidence of insufficiency.

6. Forced expiratory volume FEV1 < 50% of predicted.

7. Lactation or pregnancy.

8. History of cancer other than basal cell carcinoma of the skin or carcinoma in situ of the cervix.

9. Underlying renal disease etiology with a high risk of disease recurrence in the transplanted kidney (such as focal segmental glomerulosclerosis, type I or II membranoprolifertive glomerulonephritis).

10. Prior dose-limiting radiation therapy.

11. Known genetic disease or family history that may result in greater sensitivity to the effects of irradiation, or a physical deformity that would preclude adequate shielding or appropriate dosing during the irradiation component of the conditioning regimen.

12. Enrollment in other investigational drug studies within 30 days prior to enrollment.

13. Abnormal (>2 times lab normal) values for (a) liver function chemistries (ALT, AST, AP), (b) bilirubin, (c) coagulation studies (PT, PTT).

14. Allergy or sensitivity to any component of belatacept, ATG, tacrolimus, or rituximab.

15. Maintenance immunosuppression within 3 months prior to conditioning other than physiological doses of steroids, defined as ≤ 50 mg of hydrocortisone or dose equivalent.

16. The presence of any medical condition that the investigator deems incompatible with participation in the trial.

Donor Inclusion Criteria

1. Male or female 18–65 years of age.

2. For females of childbearing potential: a serum pregnancy test showing negative results.

3. Excellent health per conventional predonor history (medical and psychosocial evaluation).

4. Acceptable laboratory parameters (hematology in normal or near-normal range; liver function <2 times the upper limit of normal, and normal creatinine).

5. Negative for viral infection with HbsAg, HIV, HCV, or HTLV-1.

6. Cardiac/pulmonary function within normal limits (CXR, ECG).

7. Ability to understand and provide informed consent.

8. Meets standard institutional criteria for both bone marrow and kidney donation

Treatment Description

Recipients will receive a conditioning regimen that starts with Rituximab on day –7 (and days –2, 6, 13), Whole Body Irradiation 1.5 Gy x2 on study days –5 and –4, followed by ATG on Days -2, -1, 0. Belatacept 20mg/kg on Days 1, 6 and 10mg/kg on Days 13, 20 34 . Thymic irradiation (7 Gy) will be given on study day –1, and combined renal and bone marrow transplant will be done on study day 0. Prednisone will be started at 20 mg on day 10 and tapered off by day 20. Tacrolimus will be administered on study days –1 through 60, and then tapered if weaning criteria are met. Leukapheresis will be performed prior to initiating the conditioning regimen and these cells will be frozen

All patients who require a blood transfusion will receive only leukocyte-depleted and irradiated blood products for a period of at least 52 weeks following transplantation.

The proportion of patients successfully weaned off immunosuppression will be assessed.