

A Phase I Safety Trial of CD4+CD127lo/-CD25+ Polyclonal T-reg Adoptive Immunotherapy for the Treatment of Type 1 Diabetes

This is an open-label dose escalation study in which cohorts of subjects with T1DM will receive increasing doses of a single infusion of *ex vivo* selected and expanded autologous regulatory T cells (T-regs; defined as CD4+CD127lo/-CD25+ cells)

There will be 4 cohorts-Yale will only be able to participate on cohort 3 and 4 and it's expected that we will put participants on during August or September.

Primary outcome measures will be: adverse events, laboratory abnormalities and other signs of toxicity. Particular focus will be on the number and severity of infusion reactions, complications related to infection, and any potential negative impact on the course of diabetes.

Secondary diabetes-related outcome measures will include C-peptide response during mixed meal tolerance tests at 26 and 52 weeks, insulin use, and hemoglobin A1c.

Inclusion criteria:

1. Diagnosis of T1DM within >3 and <24 months of screening according to the American Diabetes Association criteria
2. Between 18 and 45 years of age
3. Positive test for Epstein-Barr antibody
4. Positive test for at least one of the following antibodies:
 - o ICA512-antibody
 - o ICA
 - o GAD65-antibody
 - o Insulin (if assessed within 10 days of the onset of insulin therapy)
 - o ZnT8
5. Peak C-peptide >0.1 pmol/ml during MMTT challenge
6. Adequate venous access to support draw of 400 ml whole blood and infusion of investigational therapy

Exclusion criteria:

1. Hemoglobin <10.0 g/dL; leukocytes <3,000/ μ L; neutrophils <1,500/ μ L; lymphocytes <800/ μ L; platelets <100,000/ μ L
2. Regulatory T cells present in peripheral blood at <10 per μ l as determined by flow cytometry
3. Serologic evidence of HIV-1 or HIV-2 infection
4. Evidence of current hepatitis B as demonstrated by HBsAg or circulating hepatitis B genomes
5. Serologic evidence of hepatitis C infection
6. Detectable circulating EBV or CMV genomes or active infection
7. Chronic use of systemic glucocorticoids or other immunosuppressive agents, or biologic immunomodulators within 6 months prior to study entry. Specifically, subjects who have received over 7 days of treatment with 7.5 mg of prednisone (or the equivalent) within 6 months prior to study entry will be excluded.
8. History of malignancy (including squamous cell carcinoma of the skin or cervix) except adequately treated basal cell carcinoma
9. Any chronic illness or prior treatment which in the opinion of the investigator should preclude participation in the trial
10. Pregnant or breastfeeding women, any female who is unwilling to use a reliable and effective form of contraception for 2 years after T-reg dosing, and any male who is unwilling to use a reliable and effective form of contraception for 3 months after T-reg dosing

Risks and Discomforts

1. **Likely**—transfusion reaction (chills, fever and/or nausea)
2. **Less Likely**
 - Infections—such as EBV or CMV. You must be EBV positive to be allowed to take part on this trial.
 - T-Regs could prevent an immune response to viruses, bacteria, parasites or fungi.
3. **Rare but Serious**
 - Lymphoproliferative Disease
 - Loss of Tumor Surveillance
 - Worsening Diabetes

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