Anti-inflammatory Therapy to Improve Outcomes After TPIAT

Inclusion Criteria:

1. Age 18-68 years.
2. Scheduled for total pancreatectomy and IAT at University of Minnesota (UM). All patients who are approved for pancreatectomy and IAT at UM are reviewed by a multi-disciplinary committee including surgeons, gastroenterologists specializing in pancreatic disease, a pain specialist, psychologist, and endocrinologist to confirm the diagnosis of chronic pancreatitis and candidate suitability for surgery.
3. Able to provide informed consent.

Exclusion Criteria:

1. Pre-existing diagnosis of diabetes mellitus, fasting blood glucose >115 mg/dl, or hemoglobin A1c level >6.0% because these are all evidence of inadequate beta-cell mass.
2. Use of any of the following in the 30 days prior to enrollment: insulin, metformin, sulfonylureas, glinides, thiazolidinediones, Glucagon Like Peptide (GLP)-1 agonists, dipeptidyl peptidase (DPP-4) inhibitors, or amylase.
3. Immunoglobulin (IgA) deficiency (serum level <5 mg/dL), which has been associated with hypersensitivity to alpha-1 antitrypsin.
4. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times the upper limit of normal (ULN). Bilirubin >ULN, unless due to benign diagnosis such as Gilbert's.
5. Known history of human immunodeficiency virus (HIV) infection, hepatitis B (chronic), or hepatitis C (chronic).
6. History of tuberculosis (TB) (latent or active disease), or positive TB skin test.
7. History of symptomatic fungal lung infection.
8. History of multiple sclerosis, transverse myelitis, Guillain Barre, or other suspected demyelinating disease, due to risk of exacerbation of these conditions with use of etanercept; or prior history of systemic lupus erythematosus 9.
9. Any of the following hematologic abnormalities: severe anemia (hgb <10 g/dL), thrombocytopenia (<150/mm3), or neutropenia (<1.0 x109/L).
10. Current use or expected use of oral or injected corticosteroids, or any medication likely to affect glucose tolerance. However, use of hydrocortisone for physiologic replacement, or use of any topical, inhaled, or intranasal glucocorticoid is permitted.
11. Current or expected use of any other immunosuppressive agent.
12. Known hypersensitivity to etanercept or A1AT.
13. Any condition that is likely, in the opinion of the patient's medical providers, to necessitate use of TNF alpha therapeutically in the future (such as psoriatic arthritis).
14. Known coagulopathy, or need for anticoagulant therapy preoperatively (coumadin, enoxaparin), or any history of pulmonary embolism. For females, plans to become pregnant or unwillingness to use birth control for the study duration.
15. Inability to comply with the study protocol.
16. Any condition that is likely, in the opinion of the patient's medical providers, to affect glucose tolerance.
17. Untreated psychiatric illness that may interfere with ability to give informed consent, or other developmental delay or neurocognitive disorder that impairs with a patient's ability to consent on their own behalf.
18. Any other medical condition that, in the opinion of the investigator, may interfere with the patient's ability to successfully and safely complete the trial.

Conditions & Interventions:

Interventions:
Drug: etanercept, Drug: Alpha-1-Antitrypsin

Conditions:
Pancreatitis, Chronic, Diabetes, Transplant

More Information

Description: SPECIFIC AIM #1: To determine if anti-inflammatory treatment with etanercept or alpha-1 antitrypsin during the critical peri-transplant engraftment period improves islet engraftment and function after islet autotransplant, as assessed by area under the curve for C-peptide on mixed meal tolerance testing (oral stimuli), acute insulin response to glucose-potentiated arginine stimulation (IV stimuli), and insulin requirements at day 90 post-transplant. The primary endpoint of the maximally stimulated acute insulin response to arginine (AIRmax) from GPAIS at day 90 will allow us to rapidly identify the most promising therapeutic agent for further development and testing in a large randomized trial.

SPECIFIC AIM #2: To gather pilot data on the long-term impact of etanercept or alpha-1 antitrypsin administered during the peri-transplant period by evaluating islet function at 1 and 2 years post-transplant, as assessed by area under the curve for C-peptide on mixed meal tolerance testing (oral stimuli), acute insulin response to glucose-potentiated arginine stimulation (IV stimuli), and insulin requirements (units/kg/day) at 1 year post-TPIAT. In addition, insulin requirements and fasting/stimulated C-peptide by MMTT will be assessed at yearly intervals from year 3-5 post-transplant. SPECIFIC AIM #3: To evaluate the mechanistic effects of etanercept and alpha-1 antitrypsin on inflammation, islet cell viability/survival, and beta cell apoptosis. This will be assessed by circulating cytokine and chemokine levels and measurement of circulating unmethylated DNA (a recently validated marker of beta cell death in T1DM) in patient serum. The goal of the current research is to select the anti-inflammatory agent with the greatest potential to preserve islet mass early after TPIAT.

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