ClinicalTrials.gov Cover Page

Title: Impact of Evolocumab (Repatha) in Cardiac Transplant Patients with Coronary Allograft Vasculopathy (CAV)

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Document: Study Protocol and Statistical Analysis Plan

Eligibility Criteria

Inclusion criteria

- Heart transplant patients 19-80 years of age
- Coronary allograft vasculopathy documented by left heart cardiac catheterization
- Able to provide signed informed consent

Note: Evolocumab will be given as add-on therapy to heart transplant patients with CAV. Patients already on statin or other lipid lowering therapy are eligible for enrollment.

Exclusion criteria

- Rejection requiring IV therapy in the prior 3 months
- Infection requiring IV therapy in the prior 3 months
- Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the upper limit of normal
- Current or recent use of a PCSK9 inhibitor within the past 12 weeks
- Dual organ transplant recipient other than heart/kidney
- Renal dysfunction defined as GFR < 20 ml/min
- Known allergy to evolocumab or its components

Randomization/Registration Procedure

Heart transplant patients will be recruited for participation solely from the University of Nebraska Heart Transplant clinic. Our program provides care for approximately 330 heart transplant patients in total, and currently performs 40-50 heart transplants per year. Of these, over 40 patients already have a known diagnosis of CAV with more expected to be diagnosed in the coming year.

Heart transplant patients with CAV will be identified by the primary investigator and the transplant cardiology team. Eligible individuals will then be invited to participate (by phone call or during a clinical appointment) by the transplant cardiology research team. Interested patients will then be referred to trained personnel for informed consent, screening and study enrollment. Coordination is expected between study enrollment and a standard post-transplant clinic appointment to facilitate participation.

This study will be an open label, single cohort study. No randomization of patients or treatment blinding will occur. Enrollment is expected to take one year, with an additional one year of follow-up resulting in a total study duration of two years.

Research Study Design

Standard post-transplant care

Heart transplant patients with CAV who primary transplant followup care at the University of Nebraska will serve as the study cohort. Given the complexity of heart transplant patients, care is highly- protocolized and organized according to graft age. Care is most intensive in the first year following transplant wherein patients are initially evaluated on a weekly basis for the first month with reduced frequency (biweekly → monthly → quarterly) based on clinical progress over the first year. During year 2 post transplant, stable post-transplant patients are typically seen quarterly and this extends to biannual evaluations during year 3. After 3 years, stable post-transplant patients can often be seen on an annual basis. Thorough evaluations are completed annually including comprehensive labwork (complete blood count, complete metabolic panel, fasting lipid panel, thyroid function tests, hemoglobin A1c, creatinine kinase, urine protein analysis), assessment for donor specific antibodies, and imaging/testing. Imaging/testing includes an annual echocardiogram and chest x-ray as well as other imaging (DEXA scan, carotid and abdominal ultrasounds) at frequencies determined by comorbidities. Immunosuppression is maintained with calcineurin inhibitors (primarily tacrolimus) and DNA synthesis inhibitors (mycophenolate mofetil, mycophenolic acid or azathioprine). Patients are switched to mTOR inhibitors (primarily sirolimus) if significant renal dysfunction develops or CAV is diagnosed. High dose steroids are started at the time of transplant and typically weaned off during the first year. Calcineurin inhibitors and mTOR inhibitors are dosed according to trough serum levels, and thus monitored at least every three months indefinitely.

CAV is diagnosed by angiography. Patients undergo a left heart cardiac catheterization annually for the first five years per standardized protocol. Beyond five years, cardiac catheterization can be alternated with a dobutamine stress echocardiogram. If the dobutamine stress test is abnormal (wall motion changes), a cardiac catheterization is completed to assess for CAV. Once patients are diagnosed with CAV, annual cardiac catheterizations are completed. Severity of CAV, once present, is based on angiographic findings as outlined in Table 3 below[1]. Of note, intravascular ultrasound can also identify CAV but is currently not used to guide management beyond changing immunosuppression regimen due to less outcome data (compared to cardiac catheterization).

Transplant patients are closely monitored for graft rejection. In general, rejection risk declines with increasing donor graft age. Surveillance endomyocardial biopsies are completed during the first year post-transplant (selected patients can undergo serum gene expression testing in lieu of endomyocardial biopsy). Donor specific antibodies are monitored on annually. Beyond one year post-transplant, rejection is detected primarily by symptoms (new onset CHF symptoms, arrhythmias or increasing fatigue) or systolic dysfunction on echocardiogram which prompts an endomyocardial biopsy.

Table 3 – ISHLT CAV nomenclature[1]

Classification	Severity	Definition
CAV-0	Nonsignificant	No detectable angiographic lesion
CAV-1	Mild	Angiographic left main <50% or Primary vessel lesion <70% or Branch stenosis <70%
CAV-2	Moderate	Angiographic left main <50% or Primary vessel lesion ≥70% or Isolated branch stenosis in 2 systems ≥70%
CAV-3	Severe	Angiographic left main ≥50% or ≥2 primary vessels with lesion ≥70% or Isolated branch stenosis in all 3 systems ≥70% or Any CAV grade with EF ≤45% or restrictive physiology

Research study design – patient enrollment and evolocumab administration

Heart transplant patients with CAV will be eligible for enrollment per inclusion and exclusion criteria listed in Section 3. The majority of heart transplant patient are on statin therapy (pravastatin is most common). Evolocumab will be given either as add-on therapy for heart transplant patients with CAV currently prescribed statin or other LDL lowering therapy, as well as those unable to tolerate lipid-lowering medications.

Study participation is expected to coordinate with the standard care of heart transplant patients. As most patients with CAV are more than 2 years post-transplant, enrollment will likely occur around the patient's annual clinical evaluation. Female patients of childbearing potential will undergo pregnancy testing prior to or during the screening/enrollment visit before study drug administration. Informed consent and baseline documentation will be completed by research personnel at the patient's annual evaluation when feasible.

Enrolled study participants will be treated with evolocumab (Repatha) 140 mg injected subcutaneously every 2 weeks for 52 weeks. All study participants will receive instruction on correct self-administration by research pharmacists. Study drug will be distributed to patients via courier or Fed Ex temperature-controlled coolers by the research pharmacy. The evolocumab dose (140 mg every 2 weeks) will remain constant for the duration of the study. Side effects will be assessed on a quarterly basis. Serious adverse events considered related to treatment, death, and pregnancy will all result in immediate discontinuation of the study drug.

Primary endpoint – LDL percentage change after 12 weeks of evolocumab therapy.

The primary objective of this study is to measure the impact of PCSK9 inhibition via evolocumab on serum LDL in heart transplant patients with CAV after 12 weeks. Similar to prior phase 2 trials investigating evolocumab, LDL change will serve as the primary endpoint providing a direct benchmark for comparison of heart transplant

patients. Baseline LDL will be obtained at study enrollment, likely with the patient's annual clinical evaluation. After 12 weeks of therapy, a fasting serum lipid profile will be obtained for measurement of LDL and assessment of the primary endpoint. Statistical analysis is detailed in Section 8 below.

Secondary endpoints

Assess the effect of evolocumab on CAV progression. All patients enrolled will have CAV documented by cardiac angiography. Standard post-transplant care includes annual angiograms in patients diagnosed with CAV to monitor for disease progression. CAV progression will be defined as an increase of one CAV grade (CAV-1 → CAV-2 or CAV-2→CAV-3). The number of patients with CAV progression of at least one grade while on evolocumab will be compared to historical controls for our transplant program. Percentage diameter stenosis for each vessel with visible CAV also will be determined by quantitative coronary angiography (QCA) using Philips Xcelera software package in a blinded fashion by an experience interventional cardiologist for patients angiograms completed one year prior to study entry, at study entry, and study conclusion. Angiographic change while on evolocumab therapy will be compared to the preceding year.

Assess the effect of evolocumab on immunosuppression regimens and graft rejection. Transplant patient are maintained on lifelong immunosuppression. These agents are prone to significant drug-drug interactions which can limit therapies. Serum levels of immunosuppression are monitored every three months per standard protocol. Measured serum levels at 3, 6, 9, and 12 months, as well as the number of dose adjustments while on evolocumab therapy while on evolocumab therapy will be compared to the preceding year. Statistical adjustment for confounding factors such as changes in renal function or other drugs known to alter immunosuppression levels (i.e. diltiazem, certain antimicrobial drugs) will be completed. In addition, the incidence of transplant rejection will be documented while on evolocumab therapy and compared to the prior year. Transplant rejection will be defined as symptoms requiring therapeutic intervention or endomyocardial biopsy findings of ≥grade 2 or positive C4d staining or new donor specific antibodies.

Measure the effect of evolocumab on serum lipids including HDL and triglycerides after 1 year of therapy. Fasting lipid profiles (total cholesterol, LDL, HDL and triglycerides) after 52 weeks of evolocumab therapy will be compared to baseline levels. Fasting lipid profiles are assessed annually as part of routine post-transplant care. The percentage change of LDL, HDL and triglyceride from baseline will be calculated after 1 year of evolocumab therapy.

Statistical analysis is detailed in Section 8 below.

Regulatory oversight

The study will be conducted under the oversight of the University of Nebraska IRB. An independent University of Nebraska Medical Center Data Safety and Monitoring Board (DSMB) will be established to monitor participant safety, data quality and evaluate the progress of the study.

Drug Formulation and Procurement

Study drug (evolocumab) will be provided by Amgen Inc. While evolocumab is commercially available and FDA approved for patient use, storage and distribution in this study will be managed by research pharmacy staff at the University of Nebraska. Study drug will be stored by research pharmacy staff who will distribute it to patients. Study participants receive study drug quarterly directly from research pharmacy staff or via courier in temperature-controlled KoolTempGTS coolers (Cold Chain Technologies, Franklin, Massachusetts). Drug accountability will be managed by research pharmacists as well.

Toxicity and Adverse Event Reporting Guidelines

Evolocumab is currently FDA-approved and commercially available for patient use in the United States. Currently used in patients for the secondary prevention of cardiovascular disease and treatment of primary hyperlipidemias, adverse event data is available from greater than 27,000 patients enrolled in clinical trials. Clinical experience has shown evolocumab to be well-tolerated with minimal adverse events (see Tables 4 and 5 below).

Adverse events will be assessed by research personnel at week 2, 4, 12, 26, 38 and study conclusion (52). Events will be obtained either by phone survey or during a standard-of-care clinic visit. Data will be stored and managed using the Forte Electronic Data Capture (EDC) software system. Adverse events will be collected using the Common Terminology Criteria for Adverse Event (CTCAE) version 5.0 forms. Adverse events will be quantified and presented by organ system. Reported events will be cataloged and reported to the University of Nebraska IRB and Amgen annually and at the conclusion of the study by research personnel. Reported events will be independently reviewed by a cardiology faculty member with significant experience prescribing PCSK9 inhibitors.

All suspected unexpected serious adverse reactions (SUSARs) related or possibly related to evolocumab and their follow-up reports will be reported to Amgen within 24 hours of submission to the regulatory agency or IRB. Amgen will be informed of any pregnancy occurring and/or existing during exposure to the investigational medicinal

product and pregnancies occurring in the partner of a patient participating in the study and potential infant exposure within ten (10) calendar days of sponsor awareness.

Section 8. Statistical Analysis Plan

Statistical analysis will be completed with the direct assistance of faculty from the University of Nebraska biostatistics department. Sample size (n=40) is chosen based on the size of the heart transplant clinic (the number of heart transplant patients with CAV expected to be eligible for study participation).

The primary outcome is percentage change from the baseline in LDL levels after 12 weeks of evolocumab therapy. Prior trials have demonstrated that evolocumab lowers LDL cholesterol at week 12 by greater than 50% from baseline[2, 3]. The sample size of n=40 is expected to yield greater than 99% power to detect 50% reduction of LDL cholesterol from baseline after 12 weeks of evolocumab therapy at a significance level of 0.05 using a two-sided Wilcoxon signed-rank test, assuming the estimated standard deviation of reduction of 0.17.

Descriptive statistics will be presented as frequencies and percentages for categorical variables, and mean ± standard deviation, or median with range for continuous variables, unless otherwise indicated. Paired t-tests or Nonparametric Wilcoxon signed-rank tests will be completed where appropriate to compare the primary endpoint before and after 12 weeks of evolocumab therapy, and compare continuous secondary endpoints after 1 year of evolocumab therapy to baseline. A linear mixed model analysis will be conducted to analyze immunosuppression serum levels measured at baseline, 3 months, 6 months, 9 months, and 1 year of evolocumab therapy. The binary secondary endpoint of CAV progression will be assessed after 1 year of evolocumab therapy using McNemar tests. Safety data will be reported with frequencies and percentages. All tests will be two-tailed. A p-value <0.05 will be considered significant. Analysis will be performed using SAS version 9.4 (SAS Institute, Cary, NC).

Given the limited statistical power due to the small cohort, conclusions from secondary endpoints are expected to by primarily hypothesis-generating with data providing support for potential future studies.