Protocol:

A randomized placebo controlled trial of inhaled beclomethasone after community-acquired respiratory viral infection in lung transplant recipients

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1. Abstract

The randomized placebo controlled trial of inhaled beclomethasone after community-acquired respiratory viral (CARV) infection in lung transplant recipients is a single center pilot study evaluating the impact of inhaled beclomethasone on the development and progression of chronic lung allograft dysfunction (CLAD) or death after CARV infection. The study will randomize 40 subjects to inhaled beclomethasone or placebo in a 1:1 ratio, and follow-up will be complete 12 months after randomization. The primary objective of the study is to determine if inhaled beclomethasone has greater efficacy than placebo for the endpoint of CLAD development or progression or death after randomization. The study will also assess multiple secondary endpoints including the safety and tolerability of inhaled beclomethasone in lung transplant recipients, respiratory viral symptom scores, the development of donor-specific human leukocyte antigen antibodies and antibodies to lung-specific self-antigens, and survival.

2. Background

Lung transplantation is the ultimate treatment for patients with advanced lung disease. However, long-term outcomes remain disappointing, and the median survival after transplantation is approximately 5.5 years. While infection and graft failure are the leading causes of death in the first year after transplantation, chronic rejection is the leading cause of death beyond the first year. Chronic rejection after lung transplantation is characterized histologically as obliterative bronchiolitis, although histologic confirmation is difficult. Therefore, chronic lung allograft syndrome (CLAD) and bronchiolitis obliterans syndrome (BOS), defined and staged based on changes in spirometry measurements, are the clinical surrogates of chronic rejection after lung transplantation. The incidence of CLAD approaches 50% at 3 years after transplantation, and there is no effective evidence-based treatment. Unfortunately, this results in a progressive and relentless decline in lung function culminating in graft failure and death. Indeed, the median survival after the diagnosis of CLAD is 3 years, and studies have consistently demonstrated a significantly reduced quality of life in patients with CLAD. Clearly, CLAD is the leading obstacle to better outcomes after lung transplantation, and lung allograft recipients urgently need strategies to prevent or delay the onset of CLAD.

The pathophysiology of CLAD has not been elucidated, but clinical risk factors have been identified and these provide insights into the underlying immunobiology. Studies have consistently identified episodes of acute rejection, lymphocytic bronchiolitis, primary graft dysfunction, donor-specific HLA antibodies (DSA), gastroesophageal reflux disease, and community-acquired respiratory viral (CARV) infections as independent risk factors for the development of CLAD. The exact mechanisms whereby CARV infection increases the risk of CLAD are unclear, but this association has been identified in both upper and lower respiratory tract infections. We have proposed that viral infection results in airway epithelial cell injury and the expression of injury-response genes that provide signals that initiate immunologic and non-immunologic pathways that result in the airway remodeling characteristic of obliterative bronchiolitis. In addition, CARV infection may increase the expression of HLA molecules in the allograft and expose cryptic self-antigens while creating the necessary inflammatory milieu for CLAD development and progression.

Systemic and inhaled corticosteroids are frequently used as anti-inflammatory agents to treat the peribronchiolar inflammation seen in viral bronchiolitis. Beneficial effects from corticosteroids have been reported, but this has not been demonstrated in lung transplant recipients.

The aim of this single center, randomized, double blind, placebo controlled study is to evaluate the short and long term effects of a 6 month course of inhaled beclomethasone on adult lung transplant recipients with CARV infection.

3. Transplant Center Experience

The study center (Barnes-Jewish Hospital / Washington University) has performed lung transplants (LTx) in over 1300 recipients since 1988. This center has long-term experience in evaluating and selecting candidates, performing transplantation, and providing high-quality follow-up. Post-transplant survival outcomes at this center are higher than the national average.

4. Study Protocol

4.1. Primary Aim

To conduct a single center, pilot, randomized placebo controlled trial that compares the efficacy and safety of inhaled beclomethasone versus placebo to prevent the development or progression of CLAD, or death after CARV infection in lung transplant recipients.

4.2. Hypotheses

Null Hypothesis	There is no difference in incidence of new or progressive CLAD, or death between the two randomized treatment groups (placebo = inhaled beclomethasone)
Alternative	There is a statistically significant difference in the incidence of new or progressive CLAD, or death between the two randomized treatment groups (placebo ≠ inhaled beclomethasone)

4.3. Study Objectives

Primary Objective

- To determine if inhaled beclomethasone has greater efficacy than placebo in preventing the composite endpoint of new or progressive CLAD or death 6 months after CARV infection in adult lung transplant recipients.

Secondary Objectives

- Incidence of new or progressive CLAD at 6 and 12 months after CARV infection
- Time to development or progression of CLAD
- Safety and tolerability of inhaled beclomethasone
- Respiratory viral symptoms
- Development of donor-specific HLA antibodies (DSA)
- Change in DSA mean fluorescence intensity
- Development of antibodies to lung-specific self-antigens (Collagen V and K-α 1 tubulin)
- Serum cytokine profiles
- Peripheral immune cell phenotypes
- Incidence of other bacterial, viral, or fungal infection at the time of CARV infection
- Incidence of acute rejection and lymphocytic bronchiolitis within 6 months following CARV infection
- Survival at 6 months (+ 10 days) and 12 months (+ 10 days) after CARV infection

4.4. Design

Single center, double blind, placebo controlled randomized trial

4.5. Setting

This single center trial will enroll 40 patients from Washington University School of Medicine and Barnes-Jewish Hospital academic lung transplant center. Screening, participant consent, treatment, and data collection will be conducted at this transplant center.

4.6. Study Population and Eligibility Criteria

The study staff will prescreen/screen all lung transplant (LTx) recipients at the institution who develop respiratory symptoms suggestive of a CARV infection. The study will only enroll a patient if he/she can come to the medical center to receive study drug. In general, the study staff will consent patients who have undergone lung transplantation, and randomize study participants (consented patients) that develop post-transplantation CARV infection. Table 1 outlines specific study eligibility criteria for enrollment and randomization. A screening log will document limited information regarding patients that undergo screening but not enrollment. Case report form (CRF)/computer data entry system will capture reason(s) for exclusion.

Table 1. Eligibility criteria for enrollment in the study

Inclusion Criteria:

- Adult (≥ 18 years old)
- Single, bilateral, or heart-lung transplant recipient
- Confirmed infection with a community-acquired respiratory virus
    - Including: adenovirus, coronavirus, influenza A or B, respiratory syncytial virus (RSV), parainfluenza virus (PiV), human metapneumovirus (hMPV), and rhinovirus/enterovirus
- At least 6 months post-transplant, with completion of 6 month surveillance bronchoscopy if indicated
- Able and willing to give written informed consent and comply with study procedures (e.g. testing, treatment)
- Able to undergo randomization and initiate study drug within 10 days of CARV infection

Exclusion Criteria:

- BOS Stage 3 [pre-CARV baseline FEV_1 < 50% of personal reference]
    - Pre-CARV baseline: the average of the 2 most recent FEV_1 separated by at least 3 weeks and also occurring within the 6 months prior to the CARV infection
        - In the event that only a single FEV_1 is available within the previous 6 months, that value will function as the pre-CARV baseline
    - Personal reference: the average of the 2 highest post-transplant FEV_1 at least 3 weeks apart
- Requirement for mechanical ventilation at study entry
- Use of inhaled steroids at the time of CARV infection
- Any condition that in the investigator's opinion would preclude the patient's participation in a clinical trial
- Lack of available spirometric data within 6 months preceding CARV infection to establish a baseline FEV_1 and/or FVC
- Pregnancy
- Current participation in another interventional clinical trial

4.7. Sampling Design

The study staff will assess all LTx recipients with a CARV infection for enrollment.

4.8. Randomization

Eligible patients who develop a CARV infection after lung transplantation will need to provide written informed consent prior to study participation and will undergo randomization using a computer-generated method with a 1:1 ratio, and stratified by BOS stage (group 1: BOS stages 0 and 0p vs. group 2: BOS stages 1 and 2) to one of the treatment assignments: (1) inhaled beclomethasone, or (2) placebo. The site will aim to randomize patients within 7 days of identification of CARV infection.

4.9. Endpoints

4.9.1. Composite Primary Endpoint

Freedom from new or progressive CLAD, or death 180 days after CARV infection.

4.9.2. Secondary Endpoints

Incidence of new and/or progressive CLAD, safety and tolerability of inhaled beclomethasone, respiratory virus symptom score, development of DSA, change in DSA mean fluorescence intensity, development of antibodies to

self-antigens, serum cytokine profiles, peripheral immune cell phenotypes, incidence of other bacterial, viral, or fungal pulmonary infections at the time of CARV infection, incidence of acute rejection and lymphocytic bronchiolitis within 6 months (+ 10) days after CARV infection, incidence of new or progressive CLAD within 12 months (+ 10) after CARV infection, and survival 6 months (+ 10 days) and 12 months(+ 10 days) after CARV infection.

4.10. Outcomes Assessment

The development of CLAD is defined according to the following criteria:

- CLAD: FEV_1 and/or FVC ≤ 80% baseline on 2 measurements obtained 3 weeks apart

Once CLAD has been established, it will be further defined by the following criteria:

- Restrictive CLAD (RAS): FVC ≤ 80% baseline on 2 measurements obtained 3 weeks apart with an FEV_1/FVC ratio ≥ 75%
- Obstructive CLAD (BOS): FEV_1 ≤ 80% baseline on 2 measurements obtained 3 weeks apart

Progressive CLAD is defined as a ≥ 15% decrement in pre-CARV infection baseline FEV_1 or FVC. The pre-CARV infection baseline FEV_1 and FVC are defined as the average of the 2 most recent FEV_1 or FVC measurements separated by at least 3 weeks, and occurring within the 6 months prior to the diagnosis of the CARV infection. In the event that only 1 FEV_1 or FVC measurement is available in the previous 6 months, that value with serve as the pre-CARV infection baseline FEV_1 or FVC.

5. Treatments

5.1. Randomized Treatment Assignment

Randomization will occur using an automated online system that will reveal assignment group only after investigator/study staff have confirmed eligibility. The system will automatically send the participant study ID number and randomized treatment group assignment to the study pharmacist.

5.2. Active or Placebo Study Drug Doses and Schedule

The study protocol plans for randomized participants to receive 6 months of active drug OR 6 months of placebo.

5.2.1. Active Study Drug

Inhaled beclomethasone (QVAR®, Teva Pharmaceuticals) 320mcg twice daily for 180 days. The first dose will be administered 7 ± 3 days after CARV infection.

5.2.2. Placebo Study Drug

The first dose of placebo for inhaled beclomethasone (provided by Teva Pharmaceuticals) will be administered 7 ± 3 days after CARV infection.

5.2.3. Packaging and Labeling of Study Drug

All packaging and labeling will be completed by the investigational drugs pharmacy. The pharmacist(s) will prepare the study drug (active therapy or placebo) for administration to randomized participants based on treatment assignment. The study pharmacist(s) will label each drug kit with the participant's study identifier information, study information, appropriate drug/placebo information, and administration instructions.

5.2.4. Handling and Dispensing

Handling and dispensing of drug will occur by the study pharmacist(s) in the investigational drugs pharmacy. The study pharmacist(s) will store the study drugs in a secure area, and they will follow local and FDA regulations. The study pharmacist(s) will ensure that the study drugs are stored in the appropriate environmental conditions. Only authorized personnel will dispense study drug, and they will follow local and FDA regulations.

5.2.5. Blinding

The study pharmacist(s) practicing in the Investigation Drugs Service will remain aware of treatment allocation/assignment. Lung transplant clinical pharmacists, non-pharmacist study staff, the participants, and those involved in clinical care or study testing will remain blinded to treatment assignment (double-dummy design).

5.3. Immunosuppression

Patients' induction and maintenance immunosuppression will be prescribed and managed according to our transplant program's standard clinical practice. Likewise, we will treat and manage acute rejection, lymphocytic bronchiolitis, and BOS according to our standard clinical practice.

5.4. Treatment of CARV Infection

The decision to institute antiviral therapy specific for CARV infection and the choice of agent will be based on our program's standard clinical practice. Influenza is generally treated with oseltamivir. Respiratory syncytial virus (RSV) and parainfluenza virus (PIV) are generally treated with aerosolized ribavirin according to our standard clinical practice. Human metapneumovirus (hMPV) is sometimes treated with aerosolized ribavirin and intravenous immunoglobulin depending on the severity of the associated illness. The study will not influence the decision to treat with specific antiviral therapy nor the choice of agents.

In addition, all patients with a decline in pre-CARV baseline FEV_1 of ≥ 10% will receive oral prednisone (1 mg/kg) orally daily (maximum of 60mg), initiated per standard protocol at the time of CARV infection. This dose will be rapidly tapered over two weeks back to the patient's pre-CARV maintenance prednisone dose.

At study entry, for the purposes of baseline CARV infection characterization, patients will receive a diagnosis of either upper or lower respiratory tract infection. Lower respiratory tract infection will be defined according to the ISHLT criteria as follows:

- ≥ 2 clinical symptoms (fever > 38 ° C, rhinorrhea, nasal congestion, sore throat, sneezing, chills/rigors, myalgia, headache) PLUS one or more of the following symptoms of lower respiratory tract involvement:
    - Cough
    - Dyspnea
    - Physical findings (one or more of the following):
        - Hypoxia (new onset or increasing)
        - New or increased O_2 requirement
        - New crackles, rales, wheezing
    - Acute respiratory distress syndrome
    - Decline in pre-CARV baseline FEV_1 by ≥ 10%
    - Viral pathogen detected from bronchoalveolar lavage specimen

6. Testing

6.1. Patient Symptom Score Card

Subjects will be asked to complete symptom score cards (Appendix 1) daily for 7 days following enrollment.

6.2. Spirometry

Subjects will have spirometry testing at the time of CARV infection and on months 1, 3, 6 and 12 (all +/- 10 days) following CARV infection. In addition, spirometry will be performed every 1-2 months (+/- 10 days) until month 12. Participants will also undergo spirometry testing when clinically indicated (new respiratory symptoms, pulmonary infiltrates, etc). Certified and trained technicians will conduct spirometry measurements according to American Thoracic Society (ATS) guidelines.

6.3. Bronchoscopy

Bronchoscopy will only be performed if clinically indicated. Surveillance bronchoscopy to evaluate for occult acute rejection is performed at 1, 2, 3, 6, and 12 months after transplantation based on our clinical practice. In addition, bronchoscopy is performed to evaluate respiratory symptoms or clinical signs of allograft dysfunction (e.g.,

hypoxemia, pulmonary infiltrates, clinically significant decrements in spirometry). Bronchoscopy will not be performed for study reasons only.

6.4. HLA Antibody Testing

Participants will be tested for the development of donor-specific HLA antibodies (DSA) at enrollment, and at months 1, 3 and 6 (± 10 days for each time point) after CARV infection using the clinical assay in our center's histocompatibility laboratory. This will require a blood draw at those time points.

6.5. Testing for Antibodies to Self-antigens and Inflammatory Cytokines

At the same time points that testing is conducted for DSA (enrollment and months 1, 3 and 6[+/- 10 days for each time point]), participants will be tested for the development of antibodies to collagen V and K-α 1 tubulin. In addition, participants' serum will be tested for a battery of pro-inflammatory and anti-inflammatory cytokines. This will be conducted in Dr. Mohanakumar's research laboratory.

7. Statistical Considerations

We estimate an incidence of new or progressive CLAD of 50% at 6 months after CARV infection in the placebo group and an absolute risk reduction of 25% in the inhaled beclomethasone group. Therefore, a sample size of 40 subjects would provide 80% power. The primary endpoint of the development or progression of CLAD or death at 6 months will be evaluated as a binary endpoint and will be analyzed using the chi-squared method. In addition, the primary endpoint will be evaluated as a time to event analysis using the Kaplan-Meier method and the two groups will be compared using the log rank test. Secondary endpoints consisting of continuous data will be analyzed using either the Student's t- test or Mann-Whitney U Test and those consisting of categorical data will be analyzed using the chi-squared method.

8. Ethical Considerations and Safety

8.1. Good Clinical Practice

Study personnel will have the appropriate qualifications related to education, training, and experience to perform study-related tasks. The study personnel will conduct the study in accordance with Good Clinical Practice (GCP), institutional review board (IRB), local and institutional guidelines.

8.2. Institutional Review Board

Prior to study initiation, the study investigator(s) will have written approval from the IRB for the protocol, consent form, and standardized written information that the study staff will provide to patients.

8.3. Informed Consent

Patients will be informed about the study and its purpose when a diagnostic nasopharyngeal swab for CARV is obtained. Eligible patients who have a positive swab result or a positive bronchoscopy specimen PCR for CARV will be approached by the study investigators. The consent process will involve a dialogue between the potential participant and the study staff. Study participation will require written informed consent from the patient. The study staff will not conduct study procedures prior to obtaining informed consent. Patients eligible for randomization will be informed that they may withdraw their consent and drop out of the study at any time point.

8.4. Adverse Events

8.4.1. Serious Adverse Event Definition

The protocol defines a serious adverse event (SAE) as any untoward medical occurrence that

- Results in death
- Threatens life (defined as an event in which the subject was at risk of death at the time of the event)
- Requires inpatient hospitalization or causes prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Results in the development of drug dependency or drug abuse
- Is a serious adverse event drug experience

All SAEs will be reviewed by the investigator to determine relationship to the study drug (definitely, likely or possibly related to the study product).

8.4.2. Site Adverse Event Collection

The study investigator and staff will monitor and evaluate for study participant SAEs. They will collect and record SAE information on the CRFs.

8.4.3. Adverse Event Monitoring and Reporting

Investigators and study staff will follow Federal and local regulations regarding SAE reporting. After randomization, the study staff at each site must report SAEs considered definitely, likely or possibly related to the study medication (as assessed by the study investigator). A study team member will complete an SAE report for all SAE events.

8.4.4. Treatment of Adverse Events

The study staff will handle any AE(s) according to clinical practice. The study personnel will implement treatment procedures and therapy in the best interest of the patient.

8.4.5. Discontinuation of Participants from Treatment

Study participants MUST discontinue study drug for any of the following reasons:

- Withdrawal of informed consent
- Any condition in which, in the opinion of the investigator, indicates that continued study drug treatment is not in the best interest of the patient.
- Termination of the study.
- Ineligibility for continued study drug treatment (Table 1)

Participants who discontinue study drug treatment should still comply with the protocol and undergo the study follow-up procedures, except for those who withdraw informed consent or become unable to freely participate in the ongoing informed consent process. CRF/computer data entry system will capture reason(s) for discontinuation and withdrawal.

9. Study Organization and Administration

9.1. Compliance

Study investigators should conduct the study as described in the protocol. Investigators should not implement deviations or change the protocol except when deemed necessary to eliminate an immediate hazard to a study participant. The investigator must document any significant deviation in the CRF and report the deviation to the IRB.

9.2. Record Keeping and Retention

The investigators must retain copies CRF and source documents for the period required by applicable regulations and guidelines, and institution procedures, whichever is longer.

9.3. Case Report Forms

Investigators and study staff should maintain adequate and accurate records. They should demonstrate consistency of data derived from source documents and CRF data, and they should explain inconsistencies.

9.4. Study Drug Records

The primary investigator at each site has the responsibility to ensure that study personnel (e.g., investigational pharmacist) maintain records of study drug disposition. Records or logs must comply with the applicable regulations and guidelines, and should include:

- Amount received
- Amount stored
- Label identification number or batch number
- Expiration date
- Dates and initials of person responsible for each investigational product inventory entry/movement
- Amount dispensed to and returned by each subject
- Non-study disposition (e.g., lost, wasted, broken)
- Amount returned to manufacturer
- Amount destroyed at study site

9.5. Return and Destruction of Study Drug

Upon completion or termination of the study, all unused and/or partially used study drug must be returned to the manufacturer or, if authorized, destroy it at the site. Returned study drug must have appropriate documentation regarding the study protocol identifier(s) and the study site.

References

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