Principal Investigator

First Name: Robert P
Last Name: Baughman
Degree:
Primary Affiliation:
E-mail: baughmrp@ucmail.uc.edu
Phone number:
Address:

City:
State or Province:
Zip or Postal Code:
Country:

General Information

Key Personnel (in addition to PI):
First Name: Robert P
Last name: Baughman
Degree: MD
Primary Affiliation: Professor Emeritus, University of Cincinnati
SCOPUS ID: 7202722744

First Name: Nelson
Last name: Kinnersley
Degree: Ph.D
Primary Affiliation: Octa Consulting Services Ltd
SCOPUS ID: 6603113772

First Name: Viswanathan
Last name: Niranjan
Degree: MD
Primary Affiliation: RxMD
SCOPUS ID: 37104599700

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: Unrestricted grant from aTyr Pharma
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2023/09/VisNiranjan_COI.pdf
https://yoda.yale.edu/wp-content/uploads/2023/09/Kinnersley_COI.pdf
https://yoda.yale.edu/wp-content/uploads/2023/10/YODA-COI-form-Baughman-updated.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00073437 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial Evaluating the Safety and Efficacy of Infliximab (Remicade) in Subjects With Chronic Sarcoidosis With Pulmonary Involvement
2. NCT00955279 - A Phase 2, Multicenter, Randomized, Double-Blind, Parallel-group, Placebo-controlled Study Evaluating the Safety and Efficacy of Treatment With Ustekinumab or Golimumab in Subjects With Chronic Sarcoidosis

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Characterisation of patients with pulmonary sarcoidosis

Narrative Summary:

We plan to use the data from two prospective, double blind trials of new biologic therapy in patients with advanced pulmonary sarcoidosis. These studies both intervened with a monoclonal antibody (directed against either tumor necrosis factor or IL-12, IL-23) versus placebo treatment. All patients were treated with standard therapy, mostly prednisone. In one study, prednisone tapering was attempted during the course of the trial.
To date, there is little information about the clinical impact of steroid and other therapy for sarcoidosis (1). These two studies provide a combined cohort of placebo treated pulmonary sarcoidosis patients. We propose to evaluate the outcome of conventional and additional therapy in these patients. By combining the data of these two trials, we will gain insight into the changes in pulmonary function such as forced vital capacity (FVC) as well as patient reported quality of life.
If feasible within the Yoda platform, we also plan to combine this information with several other placebo controlled trials (2-7). If combining patient-level data from non-Yoda trials is not possible within the Yoda platform then aggregate findings from the proposed work will be compared at the aggregate level with external trials e.g. using meta-analysis techniques &/or by the principle of Training Set and Validation Set being in different platforms
Unfortunately, there are few placebo controlled trials in sarcoidosis and studies to date have been relatively small. The ability to combine these studies will give insight into the clinical course of the disease as well as better define clinical end points in future trials (8).

Scientific Abstract:

Background:
First line treatment of symptomatic pulmonary sarcoidosis remains glucocorticoids, usually prednisone. However, long term use of glucocorticoids is associated with significant toxicity, so second line therapy with cytotoxic agents such as methotrexate are commonly recommended (1). Third line treatment is needed in at least 20% of cases. This usually is a biologic agent such as infliximab. Newer drugs are being evaluated for treating symptomatic pulmonary sarcoidosis. However, the clinical outcome of usual treatment is poorly understood. There are a limited number of placebo controlled trials in pulmonary sarcoidosis. Two of the largest trials were done by Jansenn and the data is available in this database (9;10). Information contained in the database includes pulmonary function, health related quality of life (HRQoL), and treatment. In addition, pulmonary sarcoidosis contains three major phenotypes: restrictive, obstructive, and mixed. Both studies

included patients of all three phenotypes, but analyzed the whole group. The response to therapy for the three different phenotypes may be different.
Objective:
To characterize baseline and temporal changes in patients enrolled in prospective clinical trials of interventions for use in patients with pulmonary sarcoidosis.
Study Design:
Pooling of patient-level data from randomized controlled clinical trials with ID's NCT00955279 and NCT00073437
Participants:
NCT00955279 enrolled 173 participants with chronic pulmonary sarcoidosis (lung group) and/or skin sarcoidosis (skin group) received either 180 mg ustekinumab at week 0 followed by 90 mg every 8 weeks, 200 mg golimumab at week 0 followed by 100 mg every 4 weeks, or placebo. Patients underwent corticosteroid tapering between weeks 16 and 28 (https://clinicaltrials.gov/study/NCT00955279).
NCT00073437 enrolled 139 participants with chronic sarcoidosis with pulmonary Involvement and were randomized to receive either placebo, 3 mg/kg infliximab, or 5 mg/kg infliximab infusions at weeks 0, 2, 6, 12, 18, and 24 (https://clinicaltrials.gov/study/NCT00073437)
Primary and Secondary Outcome Measure(s):
In NCT00955279 the primary end-point was week 16 change in percentage predicted forced vital capacity (ΔFVC %pred) in the lung group. Major secondary end-points were: week 28 for ΔFVC % pred, 6-min walking distance, St George's Respiratory Questionnaire (lung group), and Skin Physician Global Assessment response (skin group).
In NCT00073437 the primary endpoint was the change from baseline to Week 24 in percent of predicted FVC. Major secondary efficacy parameters included Saint George's Respiratory Questionnaire, 6-min walk distance, Borg's CR10 dyspnea score, and the proportion of Lupus Pernio Physician's Global Assessment responders for patients with facial skin involvement.
In the proposed analysis of pooled data, in addition to using the single study endpoints, additional endpoints will be defined to characterise changes over time and to evaluate subgroups of interest.
Statistical Analysis:
In addition to the Analysis of Covariance (ANCOVA) approach used on each single study, further investigation of temporal effects will be used. For example, using Mixed Models for Repeated Measures (MMRM) and Random Coefficient Regression Models (RCRM) with or without Multiple Imputation for missing data. Effects of subgroups defined by baseline characteristics will be explored with graphical approaches (e.g. forest plots) and/or use of interaction tests.

Brief Project Background and Statement of Project Significance:

Outcome of clinical trials for pulmonary sarcoidosis are poorly understood. Major endpoints have been pulmonary function (usually FVC), quality of life, and steroid dose reduction (8). Information regarding these endpoints has usually been derived from retrospective or under powered prospective studies. The two clinical trials for the use of anti-TNF therapy for sarcoidosis have been completed and results were published several years ago (9;10). The studies included a significant number of placebo treated patients monitored over 24-48 weeks. One study had a steroid tapering schedule (10).
We propose to pool the results of these two studies to examine several issues. The first issue will be the change of physiologic (including FVC) and quality of life for placebo treated patients on standard therapy for their sarcoidosis. We hope to combine this information with other placebo treated patients from other clinical trials (2-7). This would provide a better understanding of the natural course of advanced pulmonary sarcoidosis undergoing standard therapy of glucocorticoids and cytotoxic agents such as methotrexate.
We also plan to combine the findings from the proposed research with several other placebo controlled trials (2-7). We have approached the various investigators who reported these studies. We would plan on using the data from these other trials to confirm any observation made from the analysis of the two trials in YODA. For example, if we find for the YODA data that those with airway obstruction or who are Black are more likely to deteriorate while on placebo, then we will test this on the other databases. The aggregate findings from the proposed work will be compared at the aggregate level with external trials e.g. using meta-analysis techniques &/or by the principle of Training Set and Validation Set being in different platforms. This would provide a better

understanding of the natural course of advanced pulmonary sarcoidosis undergoing standard therapy of glucocorticoids and cytotoxic agents such as methotrexate.
We also propose to evaluate the clinically important difference of health related quality of life (HRQoL) of patients over time between those who have improved versus those who have worsened. For this, we would use the patient global assessment as our anchor (11). We will also explore other anchors, such as FVC. We have previously studied the clinically important differences for health related quality of life (12;13). A criticism of these prior studies was that we did not study prospectively patients while they were on a standardized treatment protocol. We believe that analysis of the two studies will give us further confidence regarding the clinically important difference for HRQoL.(14)
We are also interested in understanding the impact of steroid tapering. In one current trial (10), there was a standardized steroid tapering. Steroid withdrawal can lead to relapse of disease. We wish to analyze the impact of steroid withdrawal on HRQoL as well as physiology. In particular, we are interested in analyzing what happens with various percentages of dose reduction as well as total withdrawal. We believe an analysis at various percentages of dose reduction (as well as absolute doses) will lead to identifying a clinically important difference in designing future trials.
While sarcoidosis is an intestinal lung disease, it is associated with obstructive disease in over half of cases. In general, there are three major phenotypes of sarcoidosis: restrictive, obstructive, and mixed (14). To date, clinical trials have focused on response of the FVC, which is mostly affected by restrictive disease. We wish to determine whether treatment response and natural course of pulmonary disease is different for different phenotypes. Sharp et al (2023) recently reported findings of a retrospective study to characterize the prevalence of different pulmonary function phenotypes in a large and diverse sarcoidosis cohort from a tertiary care referral center. The authors showed "Among individuals with sarcoidosis and pulmonary function impairment, less than half demonstrated a restrictive phenotype. There were significant differences in pulmonary function phenotypes by race and sex." The authors stated that "Longitudinal studies are required to identify pulmonary function changes over time and the clinical implications of different pulmonary function phenotypes on management strategies and outcomes". The aim of this Data Request is to characterize patients enrolled in prospective clinical trials of interventions for use in patients with pulmonary sarcoidosis. In addition, we propose to examine the impact of race and sex on these changes. A further aim is to evaluate the choice of primary endpoint, for example in trials (9 & 10) FVC was the primary endpoint and the proposed work will characterise the balance of restrictive, obstructive and mixed disease which may be better served by alternative endpoints e.g. FEV1 in patients with obstructive phenotype and FVC in a restrictive phenotype.
The potential impact of findings from the proposed research is to determine the clinically important differences of HRQoL in the combined data sets. In addition, to evaluate whether the response to therapy is different for different clinical phenotypes of pulmonary sarcoidosis.

Specific Aims of the Project:

Specific Aim 1: To determine whether changes of physiology (including FEV1 and FVC) correlate with changes in quality of life for placebo treated patients on standard therapy for their sarcoidosis.
Specific Aim 2: To determine whether there are specific subgroups based on age, race, sex, or airway obstruction who are more likely to deteriorate while on placebo
Specific Aim 3: To evaluate the clinically important difference of health related quality of life (HRQoL) of patients over time between those who have improved versus those who have worsened.
Specific Aim 4: To study the impact of steroid tapering.
Specific Aim 5: To determine whether the clinical phenotype (restrictive, obstructive, or mixed) has any impact on response to therapy.

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research on comparison group

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

All randomized patients (same inclusion/exclusion as the clinical trials):
NCT00955279 enrolled 173 participants with chronic pulmonary sarcoidosis (lung group) and/or skin sarcoidosis (skin group) received either 180 mg ustekinumab at week 0 followed by 90 mg every 8 weeks, 200 mg golimumab at week 0 followed by 100 mg every 4 weeks, or placebo. Patients underwent corticosteroid tapering between weeks 16 and 28 (https://clinicaltrials.gov/study/NCT00955279).
NCT00073437 enrolled 139 participants with chronic sarcoidosis with pulmonary Involvement and were randomized to receive either placebo, 3 mg/kg infliximab, or 5 mg/kg infliximab infusions at weeks 0, 2, 6, 12, 18, and 24 (https://clinicaltrials.gov/study/NCT00073437)

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

In NCT00955279 the primary end-point was week 16 change in percentage predicted forced vital capacity (ΔFVC %pred) in the lung group. Major secondary end-points were: week 28 for ΔFVC % pred, 6-min walking distance, St George's Respiratory Questionnaire (lung group), and Skin Physician Global Assessment response (skin group).
In NCT00073437 the primary endpoint was the change from baseline to Week 24 in percent of predicted FVC. Major secondary efficacy parameters included Saint George's Respiratory Questionnaire, 6-min walk distance, Borg's CR10 dyspnea score, and the proportion of Lupus Pernio Physician's Global Assessment responders for patients with facial skin involvement.
In the proposed analysis of pooled data, in addition to using the single study endpoints, additional endpoints will be defined to characterise changes over time and to evaluate subgroups of interest.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The main predictors will be FVC, FEV-1, SGRQ, prednisone dose, patient global assessment, Race, Sex and Randomized treatment. Additional covariates may be added on an exploratory basis.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Presence/absence of Extrapulmonary involvement; Years since histologically proven sarcoidosis; Chest radiograph score; Serum angiotensin-converting enzyme; Use of concomitant medications (corticosteroids only, Immunomodulator only; both); Baseline corticosteroid dose; Baseline MRC Dyspnea score

Statistical Analysis Plan:

In addition to the Analysis of Covariance (ANCOVA) approach used on each single study, further investigation of temporal effects will be used. For example, using Mixed Models for Repeated Measures (MMRM) and Random Coefficient Regression Models (RCRM) with or without Multiple Imputation for missing data. Statistical models will include a stratification factor for the effect of study and for other factors that reflect the original randomization scheme.
Effects of subgroups defined by baseline characteristics will be explored with graphical approaches (e.g. forest plots) and/or use of interaction tests. Subgroups to be analyzed will include race, sex, age (above and below 50 at time of study entry), duration of disease prior to study entry, and

presence of airway obstruction (FEV1<70%). We will also analyze those receiving versus not receiving corticosteroids at study entry. Comparisons will be made as univariate and multi-variate analysis to determine if there is any codependence of factors. In the multivariate analyses, the importance of prognostic factors will be guided by tests of interaction (e.g. p<0.1) but since such tests have low power heuristics will also be employed. A full description and justification for the final model will be included in the report that summarizes the proposed research.

Software Used:

R

Project Timeline:

Project start October 2023; Initial analyses performed by January 2024 with follow-on analyses in the light of initial results by April 2024. Manuscript drafted by July 2024 followed by co-author reviews and revisions with submission approximately September 2024. Reporting back to YODA Project upon successful acceptance by a peer reviewed journal.

Dissemination Plan:

Peer reviewed publication(s). Target journals may include Annals of the American Thoracic Society, CHEST, European Respiratory Journal

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