

Principal Investigator

First Name: Gerhardt
Last Name: Attard
Degree: PhD
Primary Affiliation: UCL
E-mail: aimaro.wu@gmail.com
Phone number: 07490683803
Address: 72 Huntley Street

City: London
State or Province: London
Zip or Postal Code: WC1E 6EE
Country: UK

General Information

Key Personnel (in addition to PI):

First Name: Anjui
Last name: Wu
Degree: MD PhD
Primary Affiliation: University College London

First Name: Gerhardt
Last name: Attard
Degree: MD PhD
Primary Affiliation: UCL

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_awu_signed.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_attard.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. [NCT01867710 - 212082PCR2023 - A Randomized Phase 2 Study Evaluating Abiraterone Acetate With Different Steroid Regimens for Preventing Symptoms Associated With Mineralocorticoid Excess in Asymptomatic, Chemotherapy-naïve and Metastatic Castration-resistant Prostate Cancer \(mCRPC\) Patients](#)

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

Research Proposal

Project Title

Evaluation of exogenous glucocorticoid potencies

Narrative Summary:

Exogenous steroid doses for medical management are calculated from the relative glucocorticoid potencies derived from primarily rodent experiments several decades ago. The PCR2023 trial offers a unique opportunity to calculate the glucocorticoid potency of dexamethasone 0.5mg compared to three prednisolone regimens. The evaluation of bd and od prednisolone dosing allows accurate interpretation of half life. Mathematical modelling of residual steroid levels 8 and 20 weeks after initiation of continuous potent CYP17A1 inhibition calculated from 24-hour urine studies will be used to accurately define relative glucocorticoid potencies.

Scientific Abstract:

Background

Exogenous steroid doses for medical management are calculated from the relative glucocorticoid potencies derived from primarily rodent experiments several decades ago. The PCR2023 trial offers a unique opportunity to calculate the glucocorticoid potency of dexamethasone 0.5mg compared to three prednisolone regimens. The evaluation of prednisolone dosing allows accurate interpretation of half life. Mathematical modelling of residual steroid levels 8 and 20 weeks after initiation of continuous potent CYP17A1 inhibition calculated from 24-hour urine studies will be used to accurately define relative glucocorticoid potencies.

Objective

1. To construct a predictive model for mineralocorticoid excess side effects
2. To utilise individual urine steroid metabolites to compare the glucocorticoid potency of prednisone with dexamethasone in men undergoing CYP17A1 inhibition.

Study Design & Participants

Open-label, randomized clinical trial (1:1:1:1) of 164 men with mCRPC from 22 hospitals in 5 countries who were randomly assigned to 1 of 4 intervention groups between June 2013 and October 2014. Urine samples were collected at 8 and 20 weeks after the start of treatment.

Main Outcome Measure(s)

Mineralocorticoid excess (grade 1 hypokalemia or grade 2 hypertension)

Statistical Analysis

A prediction model will be built to identify patients susceptible for mineralocorticoid excess. We will use non-parametric tests to compare the glucocorticoid potency among different treatment groups.

Brief Project Background and Statement of Project Significance:

Glucocorticoids such as prednisolone or dexamethasone are used to therapeutically manage a wide range of diseases, including adrenocortical insufficiency syndromes; inflammatory conditions such as asthma, rheumatoid disorders, systemic lupus; prevention of transplant rejection. The glucocorticoid potency of dexamethasone and prednisolone were studied in mouse experiments several decades ago and these data remain the reference for endocrinologists. The NCT01867710 trial is a unique opportunity to evaluate the relative glucocorticoid potency of these two steroids in vivo in humans in whom CYP17A1 has been effectively blocked by abiraterone. These data will allow better titration of prednisolone and dexamethasone dose in the treatment of humans. This is of primary interest to the endocrine, non-cancer field but will leverage the unique situation of men treated with potent CYP17 inhibition.

Specific Aims of the Project:

To utilise individual urine steroid metabolites to compare the glucocorticoid potency of prednisone with dexamethasone in men undergoing CYP17A1 inhibition.

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

Research Methods

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

We will require the raw values for steroid urinary metabolites for all patients treated in the PCR2023 trial with associated treatment arm and demographic data (age, country of accrual), whether the patient met the primary endpoint or not (categorised by hypertension or hypokalaemia), duration of treatment, and reason for discontinuation.

Main Outcome Measure and how it will be categorized/defined for your study:

Glucocorticoid activity of 4 steroid doses measured by the level of steroid metabolites in each individual. A previously established model will be utilised to derive a score that will be derived for each individual.

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

Main predictor: mineralcorticoid excess

Independent variables: urine metabolites, clinical variables

Statistical Analysis Plan:

We will leverage the urine metabolites to build a prediction model to identify patients susceptible for Mineralocorticoid excess. The null hypothesis is that dexamethasone 0.5mg daily and prednisolone 10 daily have equivalent glucocorticoid potency. We will reject the null hypothesis if a significant difference in glucocorticoid score is observed. We will use non-parametric tests to compare the glucocorticoid score for individuals in each group. Mann Whitney u test or Wilcoxon rank sum test will be employed to compare between 2 groups. Kruskal Wallis test will be used to compare values among 3 or more groups.

Software Used:

RStudio

Project Timeline:

Data cleaning: 08/2020 - 10/2020

Data analysis: 10/2020 - 02/2021

Anticipated dates for completion of analyses: 02/2021

Preparing for manuscripts: 02/2021 - 04/2021

Results dissemination, and publication: Early May 2021

Dissemination Plan:

Publication in high-impact peer review journals (such as the Journal of Clinical Investigation or the Journal of Clinical Endocrinology & Metabolism) and presentation at international conferences (such as ENDO2021). We will coordinate with the Janssen colleagues for most appropriate publication and presentation strategy.

Bibliography:

- 1) Gerhardt Attard, Alison H. M. Reid, et al. J Clin Endocrinol Metab, February 2012, 97(2):507–516
- 2) Gerhardt Attard, et al. JAMA Oncol. 2019;5(8):1159-1167