ISRCTN41325341 https://doi.org/10.1186/ISRCTN41325341

Prednisolone in adrenal insufficiency disease

Submission date
28/01/2019

Recruitment status
No longer recruiting

Registration date
29/01/2019

Overall study status
Completed

Last Edited
11/02/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
In adrenal insufficiency (AI), the body cannot produce vital steroid hormones, the chief of which is cortisol. There are about 27,000 individuals in the UK with AI, with up to 3140 new cases per year. The main treatment is the replacement of the absent hormone with tablets. This is commonly done using hydrocortisone, taken 3 times daily. Correctly replacing the hormones is a significant challenge. If an individual is given too much hydrocortisone, they risk long-term complications including diabetes, osteoporosis (weakened bones) and cardiovascular disease (heart attacks). If, however, they are given too little, patients can feel tired, and unwell and may collapse as there is insufficient steroid hormone to cope with stress. As hydrocortisone is eliminated by the body very quickly, it must be taken three times a day to maintain adequate levels, and omitting a dose can be dangerous. This study will look at hydrocortisone as well as an alternative steroid hormone for replacement called prednisolone. Prednisolone is similar to hydrocortisone but is eliminated more slowly, requiring only once daily administration. For hormone replacement, prednisolone should be used in much smaller doses than typically used for conditions like rheumatoid arthritis. In the past, prednisolone was used in one-size-fits-all doses of 7.5 mg daily but this caused side effects such as weakening of the bones (osteoporosis) and high blood sugar (diabetes). It is now known that we can prevent these problems by the following plan: (1) we can reduce the dose required for replacement to 3-5 mg a day; (2) use a blood test to measure the amount of prednisolone remaining in the blood 8 hours after a given dose of prednisolone, we can confirm the right dose of prednisolone for each patient: 3, 4 or 5 mg. Using this plan, we can ensure that patients get the right dose of prednisolone, and minimise any side effects. This study aims to compare low-dose prednisolone with standard hydrocortisone replacement to ensure that low-dose prednisolone is equivalent to standard hydrocortisone treatment in terms of replacing the steroid hormone needs of patients with AI and in terms of maintaining their overall health.

Who can participate?
Patients aged 18 – 70 with AI

What does the study involve?
The participants are randomly allocated to treatment with either (a) 4 months of once-daily prednisolone (at the determined dose with placebo at midday and the afternoon) followed by a 2-week washout period followed by 4 months of standard thrice daily hydrocortisone, or (b) 4 months of standard thrice daily hydrocortisone followed by the same washout period and then 4

months of prednisolone. Patients and doctors do not know whether they are taking prednisolone in the first 4 months or the second 4 months as prednisolone and hydrocortisone have been specifically made for this study. During each of these 4 month periods, participants are asked to attend the study centre 3 times on Day 1, Day 30 and Day 120 for study visits. This means there is a total of 6 study visits (two 4-month study periods). During each study visit, participants attend having fasted from the night before and having taken their morning steroid tablet at an individualised fixed time. The visit involves: having measurements such as weight, heart rate, and blood pressure taken; providing a urine sample; providing a blood sample; and completing questionnaires. In all, the study visits should take no longer than 3 hours. In between the three study visits, there are also telephone consultations to follow each participant up and to ensure that they are safe.

What are the possible benefits and risks of participating?
The information from this study may help us to understand better how to treat future patients who do not produce enough steroid naturally. Participants will not benefit directly from participating in the study. We will not take any more than 450 ml of blood over a 3-month period. This is about the same amount of blood taken in a single blood donation. Furthermore, on any single visit day we will not take more than 50 ml (about 10 teaspoons). This is a safe amount of blood loss. Participants will be monitored to ensure that they do not become anaemic. As blood is being drawn in this study, there is a risk of slight pain when this is done, and a bruise may remain for a short period after blood is taken. As participants will be changing their steroid treatment as part of this study, there is a risk of undertreatment. This risk will be minimised as patients will be trialled on the new regimen if they have not previously received it before. Possible symptoms will include tiredness, dizziness, pre-syncope, syncope, palpitations, and abdominal pain. These will be detected through symptom reporting, which will take place during all visits and telephone consultations. Participants will also have a 24-hour emergency contact number for a study clinician which they will be instructed to call if they feel unwell.

Where is the study run from?
Imperial College Healthcare NHS Trust (UK)

When is the study starting and how long is it expected to run for?
January 2018 to December 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr Sirazum Choudhury, steroids@imperial.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-001502-28

Integrated Research Application System (IRAS)
201045

ClinicalTrials.gov (NCT)
NCT03936517

Protocol serial number
40936

Study information

Scientific Title
Safety and efficacy of Prednisolone in Adrenal Insufficiency Disease (PRED-AID study)

Acronym
PRED-AID

Study objectives
Low dose prednisolone and hydrocortisone as glucocorticoid replacement therapy are equivalent in efficacy and safety

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 30/01/2019, London - South East Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, United Kingdom; +44(0)207 104 8151; londonsoutheast.rec@hra.nhs.uk), ref: 19/LO/0083

Study design
Randomized controlled study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Adrenocortical insufficiency

Interventions
The method of randomisation is blocked randomisation according to type of adrenal insufficiency (primary versus secondary).
1. Four months of prednisolone once daily followed by 4 months of hydrocortisone thrice daily or
2. Four months of hydrocortisone thrice daily followed by 4 months of prednisolone once daily

The dose of the participant's usual regimen will be unchanged from their pre-study dose. The dose of the alternative medication to be used will be elucidated prior to each participant's enrolment on the study.

There is no follow up period in this study. The study duration of each participant is 9 months.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Bone health assessed by Osteocalcin concentration at Day 1, Day 30 and Day 120 of each study period

Key secondary outcome(s))
1. Bone health assessed by urinary NTX concentration at Day 1, Day 30 and Day 120 of each study period
2. Cardiovascular risk assessed by heart rate at Day 1, Day 30 and Day 120 of each study period
3. Cardiovascular risk assessed by blood pressure at Day 1, Day 30 and Day 120 of each study period
4. Cardiovascular risk assessed by waist-hip circumference at Day 1, Day 30 and Day 120 of each study period
5. Cardiovascular risk assessed by lipid profile (total cholesterol, HDL, LDL and triglycerides) at Day 1, Day 30 and Day 120 of each study period
6. Cardiovascular risk assessed by high sensitivity CRP at Day 1, Day 30 and Day 120 of each study period
7. Glycaemic handling assessed by Glucose at Day 1, Day 30 and Day 120 of each study period
8. Glycaemic handling assessed by HbA1c Day 1, Day 30 and Day 120 of each study period
9. Infection rates and severity assessed by completion of the German National Cohort Questionnaire (GNCQ) at Day 1, Day 30 and Day 120 of each study period
10. Wellbeing assessed by completion of the short form health survey-36 (SF-36) at Day 1, Day 30 and Day 120 of each study period
11. Wellbeing assessed by completion of Addisons Quality of Life questionnaire (AddiQoL) at Day 1, Day 30 and Day 120 of each study period

Completion date

14/12/2023

Eligibility

Key inclusion criteria
1. Aged 18 – 70 years
2. Male or female
3. Diagnosed with AI for over 6 months according to standard diagnostic criteria
4. Established on stable HC replacement or prednisolone replacement, dose not altered for at least 3 months
5. Established on a stable dose of Fludrocortisone, if taking, dose not altered for at least 3 months
6. Participants taking other hormone replacements (e.g. levothyroxine, testosterone or growth hormone in secondary adrenal insufficiency) are accepted providing that their replacement doses have not altered for at least 3 months
7. Participants who are otherwise healthy enough to participate, as determined by pre-study medical history and physical examination
8. Participants who are able and willing to give written informed consent to participate in the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
70 years

Sex
All

Total final enrolment
47

Key exclusion criteria
1. Participants with a diagnosis of Type 1 or Type 2 diabetes mellitus
2. Unable to give informed consent
3. Taking supplements or herbal medications that the participant is unwilling or unable to stop prior to and during the study period e.g. St John's Wort (may decrease prednisolone levels), Cat's claw, Echinacea (immunomodulatory properties)
4. Currently taking medications that alter CYP3A4 metabolism of glucocorticoids that the participant is unwilling or unable to stop prior to and during the study period e.g. phenytoin, phenobarbital, rifampicin, rifabutin, carbamazepine, primidone, aminogluethimide, itraconazole,

ketoconazole, ciclosporin or ritonavir
5. Pregnancy, taking the oral contraceptive pill, or oral oestrogen replacement therapy due to the effects on cortisol binding globulin levels and determination of prednisolone levels. Transdermal oestrogen replacement is permitted
6. Diagnosis of congenital adrenal hyperplasia, untreated

Date of first enrolment
01/02/2019

Date of final enrolment
01/02/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Imperial College Healthcare NHS Trust
Hammersmith Hospital
Du Cane Road
London
United Kingdom
W12 0HS

Sponsor information

Organisation
Imperial College of Science, Technology and Medicine

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
NIHR Academy; Grant Codes: DRF-2017-10-115

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication. The data from this study will be published in an anonymised format only. No patient identifiable data (raw data), will be available to anyone other than the researchers and the sponsor (for monitoring purposes only).

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes