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Hydroxychloroquine in ANCA Vasculitis Evaluation (HAVEN)

Submission date
17/05/2021

Recruitment status
No longer recruiting

Registration date
07/06/2021

Overall study status
Completed

Last Edited
11/04/2023

Condition category
Musculoskeletal Diseases

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

Plain English summary of protocol

Background and study aims
This study is being conducted to see if a drug called hydroxychloroquine (HCQ) can help patients with ANCA-associated vasculitis (AAV). HCQ works by reducing inflammation in people with autoimmune diseases and is used to treat conditions such as Rheumatoid Arthritis and Lupus. HCQ has been proven to be safe and effective in treating these conditions and we are hoping that using this in addition to your current therapy will better control your condition and reduce the need for high doses of steroids. Participants of this study will receive either HCQ or dummy pills (placebo) to take daily for 12 months. We are inviting 76 patients with AAV to take part.

Who can participate?
Patients with Granulomatosis Polyangiitis (GPA), Microscopic Polyangiitis (MPA), or Eosinophilic Granuomatosis with Polyangiitis (also known as Churg-Strauss Syndrome) are invited to participate.

What does the study involve?
The study involved being allocated to receive either HCQ or placebo (dummy) pills by chance, by a computer. Patients and study doctors will not know which treatment is being given to each patient. Patients will be asked to take these pills every day for a year, along with their usual treatments. This will include steroids (prednisolone). The study doctors will aim to gradually reduce the dose of steroids along the course of the study. There are 10 visits over the course of the year and each visit involves a number of assessments, including additional blood samples for research purposes.

What are the possible benefits and risks of participating?
Patients are asked to attend the hospital more frequently than they would do if they chose not to take part. Where possible, these visits will align with their usual appointments. Patients will be reimbursed for their travel costs. They will also receive more regular input from a study nurse and doctor to closely monitor and help you manage their vasculitis. If they are in the group that receives HCQ, it is possible that it will help their vasculitis. However, we cannot say this for certain until we have completed this and future studies. Patients may not directly benefit from taking part in this study, but the information gained from their participation may help to improve the treatment of patients with their condition in the future. There may be bruising and

discomfort at the site of the blood tests, as with any blood test. However, and where possible, the blood taken for research purposes will be collected at the same time as their routine blood tests to minimise discomfort.

Where is the study run from?
Guy's and St Thomas' NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January 2019 to March 2025

Who is funding the study?
The Medical Research Council (UK)

Who is the main contact?
Prof David D'Cruz
david.d'cruz@kcl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof David D'Cruz

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Additional identifiers

EudraCT/CTIS number
2018-001268-40

IRAS number
251987

ClinicalTrials.gov number
NCT04316494

Secondary identifying numbers
CPMS 44298, IRAS 251987

Study information

Scientific Title
Hydroxychloroquine in ANCA Vasculitis Evaluation (HAVEN): a multicentre, randomised, double-blind, placebo-controlled trial

Acronym
HAVEN

Study objectives
The addition of hydroxychloroquine to background therapy improves clinical response and quality of life in patients with ANCA-associated vasculitis (AAV).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/01/2020, - London - Riverside Research Ethics Committee (Level 3 Block B, Whitefriars, Lewins Mead, Bristol BS1 2NT; +44 (0)207104 8204; nrescommittee.london-riverside@nhs.net) ref: 20/LO/0028

Study design
Multicentre double-blind randomized placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional file ISRCTN79334891_PIS_v2.1_12Oct2020 (added 07/06/2021)

Health condition(s) or problem(s) studied
Microscopic polyangiitis, ANCA vasculitis

Interventions
Participants who have Granulomatosis with Polyangiitis, Microscopic Polyangiitis or Eosinophilic Granulomatosis with Polyangiitis will be recruited from 10 sites over 2 years. Participants will be randomised in a 1:1 ratio of hydroxychloroquine or placebo. Neither the patient nor the research team will know which treatment group the participant is in.

Randomisation will be via a bespoke web-based randomisation system hosted by the King's Clinical Trials Unit. Authorised site staff will be allocated a username and password for the randomisation system via the Trial Manager. An authorised staff member will log into the randomisation system (www.ctu.co.uk), click ‘randomisation’ and select ‘HAVEN’, and enter the patient’s details, including the unique PIN. Once a patient is randomised, the system will automatically generate emails to key staff within the study. Additional blinded emails may be generated from the randomisation system to key trial site staff depending on their role in the study. Data will be exported upon request and passed to the trial statistician. Data will be exported upon request and passed to the trial statistician. Data may be exported in blinded, subgroup blinded, or unblinded formats. Patients will be randomised with minimisation for: ANCA (positive vs negative), age (</≥ 60 years), rituximab treatment and smoking status (smoking reduces hydroxychloroquine effectiveness by inducing cytochrome P450 enzyme) to ensure the groups are balanced.

Once the participant agrees to take part and has signed informed consent, they will undergo the following assessments, tests, and procedures to find out if they can take part in the study. Some may be routinely done by the study doctor as part of regular vasculitis care even if the participants are not in the study:
1. Medical history
2. Birmingham Vasculitis Activity Score (BVAS)
3. Physical exam
4. Blood tests
5. Pregnancy test
6. Urine drug test
7. Electrocardiogram
8. Arrange for optician review

If the patient is eligible to take part in the study, they will be randomised to receive either hydroxychloroquine or a placebo in addition to background medication. Participants will receive 2 tablets to take once a day over the course of a year. Participants may have their dose reduced to 1 tablet dependent on their weight at baseline and renal function. All participants will have their prednisolone dose tapered down over the course of the study. Participants will be asked to fill in a patient diary on a weekly basis to record whether they've taken their medication and if they've experienced any change of symptoms.

Participants will be asked to attend the hospital at weeks 4, 16, 28, 40, 44, 48, 52, and 56. At each of these visits, participants will undertake some or all of the following tests/assessments:
1. Physical exam including visual acuity
2. Weight and vital signs
3. BVAS assessment and Vasculitis Damage Index (VDI)
4. Patient questionnaires
5. Any changes to their medicines and health status
6. Side effects
7. Blood samples and urine tests to see how the study drug is affecting the body

Participants will also be asked to undergo an electrocardiogram (ECG) at two of the visits.

Patients will be followed up by phone in weeks 10, 22, and 34. This phone call will be based on the AAV Pro Questionnaire and patients will also be encouraged to report any adverse events. Patients reporting new or worsening symptoms will be invited to the hospital for an unscheduled visit.

In addition to clinical blood samples, 76 ml of blood will be taken for research purposes for all participants. These will be taken at the same time as clinical bloods to minimise discomfort for the participant. Participants at Guy's and St Thomas' will have an additional 200 ml of blood taken for isolation of cells. These bloods will be stored and kept for future research, with the written consent of the participant.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
hydroxychloroquine

Primary outcome measure
Percentage of patients with uncontrolled AAV disease activity measured using Birmingham Vasculitis Activity Score (BVAS), prednisolone dose records, and medication records at 44, 48, 52, and 56 weeks. Uncontrolled AAV is defined as one of the following:
1. BVAS >3)
2. BVAS ≤3, but prednisolone for AAV >7.5 mg daily
3. BVAS ≤3, but corticosteroid use for any reason >7.5 mg daily at any point during the final 12 weeks of the study (±7 days). Inhaled corticosteroids will not contribute to the primary endpoint, nor will methylprednisolone given for rituximab maintenance therapy.

Secondary outcome measures
1. Cumulative number of visits where BVAS=0 (excluding screening, baseline and week 56) measured using Birmingham Vasculitis Activity Score (BVAS) at 4, 16, 28, 40, 44, 48, and 52 weeks
2. Proportion of patients with treatment failure at week 52 measured from the incidence of death due to vasculitis disease activity or a severe disease flare resulting in organ failure or critical care admission at 52 weeks
3. Cumulative prednisolone dosage measured using prednisolone dose records at baseline, 4, 16, 28, 40, 44, 48, 52, and 56 weeks
4. Total number of adverse events measured using adverse event records at baseline, 4, 10, 16, 22, 28, 34, 40, 44, 48, 52, and 56 weeks
5. Total number of infections per patient measured using physician history and examination, and investigations at baseline, 4, 16, 28, 40, 44, 48, 52, and 56 weeks
6. Total number of vasculitis flares per patient (excluding screening, baseline and week 56) measured using BVAS at 4, 16, 28, 40, 44, 48, and 52 weeks
7. Time to remission measured using BVAS at baseline, 4, 16, 28, 40, 44, 48, 52, and 56 weeks where BVAS =0 on two consecutive visits
8. Time to first limited flare measured using BVAS at baseline, 4, 16, 28, 40, 44, 48, 52, and 56 weeks where a new or worsening minor item is present on the BVAS with no new major items
9. Time to first severe flare measured using BVAS at baseline, 4, 16, 28, 40, 44, 48, 52, and 56 weeks where a new or worsening major item on the BVAS is present
10. Proportion of patients categorized as having a severe flare at each time point in the trial schedule (excluding screening, baseline and week 56) measured using BVAS at 4, 16, 28, 40, 44, 48, and 52 weeks
11. Proportion of patients categorized as having a limited flare at each time point in the trial schedule (excluding screening, baseline and week 56) measured using BVAS at 4, 16, 28, 40, 44,

48, and 52 weeks
12. Absolute values and relative change from baseline in the Vasculitis Damage Index (VDI) at each time point in the trial schedule measured using VDI at baseline, 16, 28, 44, and 52 weeks

Exploratory outcomes:
1. Incidence of new diabetes mellitus measured using blood samples at baseline, 4, 16, 28, 40, 44, 48, 52, and 56 weeks
2. Prevalence of dyslipidaemia measured using blood samples at baseline, 28, and 52 weeks
3. Fatigue measured using FACIT score at baseline, 16, 28, 44, 52, and 56 weeks
4. Quality of life measured using the Short Form-36 (SF-36), EuroQol 5-dimension (EQ5D), and Health Assessment Questionnaire (HAQ) questionnaires at baseline, 16, 28, 44, 52, and 56 weeks, and ANCA-associated vasculitis patient-reported outcome (AAV PRO) at baseline, 10, 16, 22, 28, 34, 44, 52, and 56 weeks
5. Glucocorticoid toxicity measured using the Glucocorticoid Toxicity Index (GTI) at baseline, 28, and 52 weeks
6. Disease severity measured using the Physician's Global Assessment (PGA) at baseline, 4, 16, 28, 40, 44, 48, 52, and 56 weeks
7. ANCA titres measured from blood samples at baseline, 16, 28, 40, 52, and 56 weeks
8. Proportion of patients with medicine compliance of ≤80% (see section 8.10) measured using medication review at baseline, 4, 10, 16, 22, 28, 34, 40, 44, 48, 52, and 56 weeks
9. Absolute values and relative change from baseline in the renal variables: serum creatinine, serum albumin, urine protein: creatinine ratio at each time point outlined in the trial schedule measured using blood samples at baseline, 4, 16, 28, 40, 52, and 56 weeks

Overall study start date
01/01/2019

Completion date
31/03/2025

Eligibility

Key inclusion criteria
Patients:
1. Aged ≥18 years at screening
2. Clinical diagnosis of Granulomatosis Polyangiitis (GPA), Microscopic Polyangiitis (MPA), or Eosinophilic Granulomatosis with Polyangiitis (EGPA) according to the Chapel Hill criteria
3. Birmingham Vasculitis Activity Score (BVAS v.3) >3 with minor BVAS items only (no major BVAS items) at screening and randomisation
4. Receiving maintenance therapy at a stable dose for 4 weeks prior to randomisation
5. If receiving corticosteroids for reasons other than vasculitis must be on a stable regimen for 4 weeks prior to randomisation
6. Not pregnant or nursing. Is either: not of non-childbearing potential, for example, is postmenopausal (1 year without menses), or has had a hysterectomy, bilateral oophorectomy, documented tubal ligation, or other permanent sterilization procedure; or is of childbearing potential and has a negative urine pregnancy test at screening and at baseline and agrees to using an effective method of contraception. Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Partcipants of childbearing potential must consistently and correctly use of one of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:

6.1. Oral contraceptive, either combined or progestogen alone
6.2. Injectable progestogen
6.3. Implants of levonorgestrel or etonogestrel
6.4. Estrogenic vaginal ring
6.5. Percutaneous contraceptive patches
6.6. Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label
7. No contraindications to hydroxychloroquine therapy and normal baseline visual fields at screening
8. Willing and able to give written informed consent to participate in the trial
9. Patients should have sufficient understanding of the English language to provide informed consent and complete the patient questionnaires
10. Negative urine drug screen should be performed prior to study entry

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 76; UK Sample Size: 76

Key exclusion criteria
1. Currently taking hydroxychloroquine or related antimalarial such as mepacrine or chloroquine
2. Estimated Glomerular Filtration Rate (eGFR) <30 ml/min
3. Weighing <40 kg
4. Sensitivity, anaphylaxis, or allergy to hydroxychloroquine or any other 4-aminoquinoline compound
5. Known glucose-6-phosphate dehydrogenase deficiency
6. Known lactose intolerance
7. Evidence of plaque psoriasis
8. Concomitant use of the following medications:
8.1. Tumour necrosis factor inhibitor treatment (e.g. etanercept)
8.2. Cyclophosphamide
8.3. Abatacept
8.4. Alemtuzumab
8.5. Any experimental or biological therapies
8.6. Intravenous, intramuscular or sub-cutaneous immunoglobin
8.7. Plasma exchange
8.8. Antithymocyte globulin
8.9. Tamoxifen
8.10. Live vaccines
9. B cell depleting therapy (rituximab) for remission induction. Rituximab maintenance therapy is permitted.

10. Severe or rapidly progressive ANCA vasculitis with at least one major Birmingham Vasculitis Activity Score (BVAS) item
11. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to vasculitis (i.e. cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy, or infectious disease) which, in the opinion of the principal investigator, could confound the results of the study or put the patient at undue risk
12. Have a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix
13. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to randomisation
14. Have a historically positive test, or test positive at screening,for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody, or are known to be HIV-1 positive
15. Have a Grade 3 or greater laboratory abnormality based on the CTCAE toxicity scale (version 5), unless considered by the investigator to be related to the underlying disease or induction therapy
16. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results, including QT interval corrected using the same consistent formula at each visit (QTc) of >470 msec (female participants) or >450 msec (male participants) demonstrated by at least two ECGs.
17. Participation in any other interventional trial within the last 6 months
18. Current symptomatic COVID-19 infection
19. Have been admitted to the ICU in the past 6 months due to a COVID-19 infection

Date of first enrolment
17/12/2020

Date of final enrolment
30/09/2023

Locations

Countries of recruitment
England

United Kingdom

Wales

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
Trust Offices Guy's Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre

Cardiff & Vale University LHB
Corporate Head Quarters
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
University Hospitals Of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Oxford
United Kingdom
OX3 9DU

Study participating centre
Royal Berkshire NHS Foundation Trust
Royal Berkshire Hospital

London Road
Reading
United Kingdom
RG1 5AN

Study participating centre
Royal Glamorgan Hospital
Ynysmaerdy
Llantrisant
United Kingdom
CF72 8XR

Study participating centre
South Tyneside and Sunderland NHS Foundation Trust
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Surrey and Sussex Healthcare NHS Trust
Trust Headquarters
East Surrey Hospital
Canada Avenue
Redhill
United Kingdom
RH1 5RH

Study participating centre
Epsom and St Helier University Hospitals NHS Trust
St Helier Hospital
Wrythe Lane
Carshalton
United Kingdom
SM5 1AA

Study participating centre
Royal United Hospital
Combe Park
Bath

United Kingdom
BA1 3NG

Study participating centre
Torbay and South Devon NHS Foundation Trust
Torbay Hospital
Newton Road
Torquay
United Kingdom
TQ2 7AA

Study participating centre
Liverpool University Hospitals NHS Foundation Trust
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
Maidstone and Tunbridge Wells NHS Trust
The Maidstone Hospital
Hermitage Lane
Maidstone
United Kingdom
ME16 9QQ

Study participating centre
East and North Hertfordshire NHS Trust
Lister Hospital
Coreys Mill Lane
Stevenage
United Kingdom
SG1 4AB

Study participating centre
University Hospitals Sussex NHS Foundation Trust
Worthing Hospital
Lyndhurst Road

Worthing
United Kingdom
BN11 2DH

Sponsor information

Organisation
Guy's and St Thomas' NHS Foundation Trust

Sponsor details
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16th Floor
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Sponsor type
Hospital/treatment centre

Website
http://www.guysandstthomas.nhs.uk/Home.aspx

ROR
https://ror.org/00j161312

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. The Chief Investigator will ensure that the results are analysed, written up, reported and disseminated upon completion of the trial. No personal data will be shared.

Intention to publish date
30/09/2025

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.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v2.1	12/10/2020	07/06/2021	No	Yes
Protocol file	version v4.0	21/08/2020	07/06/2021	No	No
Protocol article		06/04/2023	11/04/2023	Yes	No
HRA research summary			26/07/2023	No	No