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A pilot study to assess shortened therapy for hepatitis C infected adults in Vietnam

Submission date
16/07/2018

Recruitment status
No longer recruiting

Registration date
17/09/2018

Overall study status
Completed

Last Edited
10/01/2023

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Hepatitis C is a virus that causes infection of the liver. Over time (many years) the virus damages the liver through causing inflammation and scarring. Eventually, patients can develop liver failure and liver cancer. There are slightly different types of the hepatitis C in different places around the world. In Vietnam, the most common types are called genotype 1 and genotype 6. Recently, there has been great progress in improving treatment of hepatitis C because of the development of drugs called DAAs (direct acting antivirals). DAAs can cure hepatitis C in the vast majority of patients, which is defined as HCV can no longer being detected in the patient's blood. It is thought that when the virus is no longer detectable in blood, then the patient is no longer at risk of liver failure or cancer. However, DAAs have not been used much in patients with infections caused genotype 6 HCV. Because genotype 6 infections are common in Vietnam, it is important to make sure that these new DAAs work in Vietnam.
One of the problems with HCV treatment is that the medication needs to be taken every day for 12 weeks. However, it is likely that shorter courses of treatment, that would be easier for patients to complete, are just as effective. This study aims to improve treatment of hepatitis C virus (HCV) infection by testing whether shorter courses of treatment are effective in some patients, and to show that this treatment also works in Vietnam.

Who can participate?
Adult patients with a chronic HCV infection attending the outpatient hepatitis clinic at the Hospital for Tropical Diseases

What does the study involve?
This study is an outpatient study which will involve attending a clinical regularly at the Hospital for Tropical Diseases. At each visit the patient will see the study doctors who will assess the patients response to treatment and perform any blood tests needed for the study. This will include blood tests to measure the amount of HCV in the blood, and the amount of DAA drugs in the blood.
In this study, we will enroll 2 kinds of patients – those with mild HCV infections (no evidence of liver damage yet), and those with cirrhosis (evidence of liver scarring due to the HCV infection). In the first group of patients, we will measure the amount of HCV in their blood 48 hours after starting treatment. Patients who do not have any HCV detectable in their blood at this

timepoint will have shortened treatment and will continue their DAA treatment until 4 (rather than the usual 12) weeks treatment has been completed. The patients will be followed up in clinic in line with standard practice to ensure they remain cured. If they are not cured they will be offered re-treatment with 12 weeks of treatment.
For the second group of patients, we will measure the amount of HCV in their blood 14 days after starting treatment. Patients who do not have any HCV detectable in their blood at this timepoint will continue their DAA treatment until 12 (rather than the usual 24) weeks treatment has been completed. The patients will be followed up in clinic in line with standard practice to ensure they remain cured. If they are not cured they will be offered re-treatment with 24 weeks of treatment.

What are the possible benefits and risks of participating?
The benefits of participating in the study are that all treatment and monitoring will be provided free for the participants, including compensation for travel costs for attending the study. The treatment is likely to cure the patients of HCV, but there may be a small risk of lower overall cure rates in patients who receive shorter treatment courses. Therefore, if a patient received shortened treatment because of a good initial response, but then did not clear the HCV from their blood, they will be offered free retreatment for 12 (mild cases) or 24 (cirrhosis) weeks. Being in the study will result in some additional blood tests. Blood tests are taken using a need from a vein in the arm and this can be uncomfortable and occasionally result in bruising.

Where is the study run from?
Trial study centre: Hospital for Tropic Diseases, Ho Chi Minh City (Vietnam)
Trial run from:
1. Imperial College London (UK)
2. University of Oxford (UK)
3. Oxford University Clinical Research Unit, Ho Chi Minh City (Vietnam)

When is study starting and how long is it expected to run for?
April 2017 to September 2021

Who is funding the study?
1. Global Challenges Research Fund (GCRF) (UK)
2. UK Medical Research Council (MRC) (UK)

Who is the main contact?
1. Imperial College: Professor Graham Cooke (g.cooke@imperial.ac.uk)
2. Oxford University Clinical Research Unit: Professor Jeremy Day (jday@oucru.org)
3. Hospital for Tropical Diseases: Dr Nguyen Van Vinh Chau (chaunvv@oucru.org)

Contact information

Type(s)
Scientific

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Type(s)
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700000

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
33CN, 106680/Z/14/Z

Study information

Scientific Title
SEARCH-1 - South East Asian Research Collaboration on Hepatitis

Acronym
SEARCH-1

Study objectives
Shortened HCV treatment courses based on early viral responses to sofosbuvir and daclatasvir therapy will achieve high rates of cure

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 12/10/2018, Ethical Evaluation Commitee in Biomedical Research of Ministry of Health, Vietnam (138A Giang Vo, Ba Dinh, Ha Noi, Viet Nam; (+84) 0462732156; admin@iecmoh.vn), ref: 6172/QĐ-BYT
2. Approved 04/10/2018, Oxford Tropical Research Ethics Committee, UK (University of Oxford Research Services, University Offices, Wellington Square, Oxford OX1 2JD; +44 (0) 1865 (2) 82106; oxtrec@admin.ox.ac.uk); ref: 43-17
3. Approved 07/06/2018, Hospital for Tropical Diseases Ethics Commitee, Vietnam (764 Vo Van Kiet, ward 1, district 5, HCMC, Viet Nam; (+84) 28 3923 8704; bv.bnhietdoi@tphcm.gov.vn), ref:

CS/BND/18/25
4. Approved 18/12/2018, Imperial College Research Ethics Committee, UK (Level 2, Medical School Building, St Marys Campus, London W2 1PG; +44 (0)207 594 9484; researchethicscommittee@imperial.ac.uk), ref: 17IC4238

Study design
Interventional non-randomised single-arm open label trial

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Chronic hepatitis C virus (genotypes 1 and 6)

Interventions
Participants will be recruited in Ho Chi Minh City, Vietnam at the Hospital for Tropical Diseases. Potential participants will be identified and approached by clinic staff to participate in the trial. In addition, appropriate patients who are part of the Hepatitis Cohort will be approached for participation in line with previous permissions.
There are two treatment arms: the mild liver disease arm and the compensated cirrhotic arm. Each participant in the two arms will be treated with the same drug combination (sofosbuvir (SOF) 400mg and daclatasvir (DCV) 60mg orally, taken daily), but with differing durations of therapy. The duration of first-line SOF/DCV treatment will be determined by the initial response to treatment.
For mild liver disease arm, all individuals will have their HCV RNA load assayed at enrolment and 24 and 48 hours after initiation of therapy (first dose to be taken in the clinic at day 0). For participants with viral load <500 IU/ml at 48 hours (day 2 visit), treatment will be complete 4 weeks of therapy. All other participants will receive 8 weeks of therapy. Following cessation of first line therapy (at the end of treatment (EOT) visit), all participants will have HCV viral load assayed twice weekly for 4 weeks. Participants meeting the definitions of first line failure will be eligible for retreatment with the same drug combination for 12 weeks at any time after EOT +2 weeks.
For the arm consisting of patients with compensated cirrhosis, participants who have achieved virological suppression (HCV RNA load <500 IU/ml) by 14 days after initiating treatment will complete 12 weeks of therapy. Those who do not achieve virological suppression will continue to complete 24 weeks of therapy. Following completion of first line therapy, all participants will have HCV viral load assayed every four weeks for 12 weeks.
The study follow-up completes at 12 weeks after the end of treatment, or re-treatment, for all

patients. Following study participation, all patients will return to normal standard of care follow-up within the hospital where they will undergo follow-up for up to 2 more years according to national guidelines.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Sofosbuvir (SOF) and daclatasvir (DCV)

Primary outcome measure
Sustained virological response (SVR12), defined as plasma HCV RNA < LLOQ (lower limit of quantification, < 15 IU/ml), 12 weeks after the end of first treatment without prior failure, defined as either:
1. 2 consecutive measurements of HCV RNA > LLOQ, taken at least 1 week apart, after 2 consecutive visits with HCV RNA < LLOQ at any time. The latter confirmatory measurement must be > 2000 IU/ml
2. 2 consecutive measurements of HCV RNA, taken at least 1 week apart, that are > 1 $\log_{10}$ increase above HCV RNA nadir on treatment and > 2000 IU/ml at any time

Secondary outcome measures
1. Sustained virological response (SRV) after the end of the combined first treatment phase and any re-treatment phases (only applicable to mild patients), defined as per primary outcome measure
2. Lack of initial virological response in which measurements of HCV RNA (at any time, taken at least 1 week apart from baseline) are <1 $\log_{10}$ decrease in the HCV RNA load from baseline
3. All clinical grade 3 or 4 adverse events, serious adverse events, and all adverse reactions, recorded on the case report form from the start of the trial to 12 weeks after the end of treatment
4. Adverse events of any grade leading to change in treatment (SOF, DCV or any other medication), recorded on the case report form from the start of the trial to 12 weeks after the end of treatment
5. Adverse reactions (any grade) (considered definitely/probably/possibly related to SOF or DCV), recorded on the case report form from the start of the trial to 12 weeks after the end of treatment
6. Grade 3 haemoglobin decreases, defined as Hgb <8.0 g/dL, <4.9 mmol/L and <80 g/L. For stratum A first line and stratum B participants, this is assessed at the baseline, day 28, at the end of treatment, and 12 weeks after the end of treatment (day 84). For the stratum A re-treatment participants, this is assessed at the baseline, week 4, end of treatment and week 24 (end of treatment for this stratum).
7. Grade 3/4 increases in total bilirubin. For stratum A first line and stratum B participants, this is assessed at the baseline, day 28, at the end of treatment, and 12 weeks after the end of treatment (day 84). For the stratum A re-treatment participants, this is assessed at the baseline, week 4, end of treatment and week 24 (end of treatment for this stratum).
7.1. Grade 3 defined as >3.0 - 10.0 x ULN if baseline was normal OR >3.0 - 10.0 x baseline if baseline was abnormal
7.2. Grade 4 defined as >10.0 x ULN if baseline was normal OR >10.0 x baseline if baseline was abnormal

Overall study start date
01/04/2017

Completion date
13/09/2021

Eligibility

Key inclusion criteria
For all participants enrolled in Stratum A (mild disease) or Stratum B (cirrhosis):
1. Aged 18 years or older
2. At least one detectable viraemia prior to the screening visit (by quantitative HCV RNA, qualitative assay or HCV genotype), with no intervening undetectable results
3. Plasma HCV RNA >LLOQ at screening
4. BMI of 18 kg/m² or greater
5. Laboratory tests:
5.1. Creatinine clearance (estimated using Cockcroft-Gault) ≥ 60 ml/min,
5.2. International normalised ratio (INR) <1.5xULN
6. Written informed consent obtained from the patient

For Stratum A, additional inclusion criteria are:
1. Infected with HCV genotype 1 (all subtypes) or genotype 6 (all subtypes)
2. Mild liver disease: No evidence of significant liver fibrosis resulting from any aetiology, defined as one of the following:
2.1. Fibroscan score ≤7.1 kPa, equivalent to F0-F1 [19], within 180 days prior to planned enrolment (Fibroscan must be a valid result (based on at least 10 readings) performed by an experienced (as evidenced by CV and/or training logs) technician)
2.2. Biopsy consistent with mild fibrosis (Ishak score ≤ 2/6) within 180 days prior to planned enrolment

For Stratum B, additional inclusion criteria are
1. Infected with HCV genotype 6 (all subtypes)
2. Compensated Cirrhosis: Evidence of compensated cirrhosis resulting from any aetiology defined as one of the following:
2.1. Fibroscan* score ≥10.1 kPa within 180 days prior to enrolment
2.2. Biopsy consistent with cirrhosis (Ishak score ≥5/6 or equivalent) within 180 days prior to enrolment)
2.3. Imaging (Ultrasound or CT or MRI) reported as showing cirrhosis
3. Childs-Pugh Score ≤7 according to the following (the preceding number in brackets indicates the score for each factor):
3.1. Bilirubin (µmol/l):
(1) < 34.2
(2) 34.2 - 51.3
(3) > 51.3
3.2. Albumin (g/l):
(1) > 35
(2) 28-35
(3) < 28
3.3. INR:
(1) < 1.7
(2) 1.7 - 2.2

(3) > 2.2
3.4. Ascites:
(1) Absent
(2) Slight
(3) Moderate
3.5. Encephalopathy:
(1) None
(2) Grade 1-2
(3) Grade 3-4
* Fibroscan must be a valid result (based on at least 10 readings) performed by an experienced (as evidenced by CV and/or training logs) technician.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
In total, 103 participants will be recruited, stratified by stage of liver disease. 60 participants will be recruited with mild liver disease (30 genotype 1, 30 genotype 6; all HIV negative). 43 participants will be recruited with compensated cirrhosis (genotype 6 only; HIV negative or HIV positive).

Total final enrolment
93

Key exclusion criteria
1. Previous Hepatitis C (treatment with DAAs, and/or pegylated-interferon and/or ribavirin)
2. HIV infected
3. Solid Organ Malignancy within 5 years prior to screening
4. Any condition in the judgement of the investigator which might limit the patient's life expectancy within the duration of the study
5. Any disorder or circumstance which in the opinion of the investigator may have a significant negative impact on the ability of the patient to adhere to the trial regimen
6. HBsAg positive
7. Disorder which may cause ongoing liver disease including, but not limited to, ongoing alcohol misuse
8. Currently receiving medication known to interact with study medications for which dose adjustment for daclatasvir or sofosbuvir would be recommended in the Summary of Product Characteristics.
9. Use of other investigational products in clinical studies within 60 days of screening
10. History of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months
11. Patients currently using amiodarone or other anti-arrhythmics (including patients with

permanent pacemakers).
12. Pregnancy
13. Symptomatic haemoglobinopathy (e.g. thalassemia major, sickle-cell anaemia).
14. Unlikely to be able to attend follow-up visits for any reason, as judged by the attending physician

Date of first enrolment
11/02/2019

Date of final enrolment
30/04/2020

Locations

Countries of recruitment
Viet Nam

Study participating centre
Hospital for Tropical Disease
764 Vo Van Kiet, Ward 1, District 5
Ho Chi Minh city
Viet Nam
700000

Sponsor information

Organisation
Imperial College London

Sponsor details
St Mary’s Campus
Praed Street
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SW7 1NA

Sponsor type
Research council

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Research council

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

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
01/02/2022

Individual participant data (IPD) sharing plan
Clinical data and clinical laboratory data will be entered into CliRes, a Title 21 Code of Federal Regulations (CFR) Part 11-compliant data capture system provided by the OUCRU IT department. CRFs, and administrative documentation will be kept in a secure location and held

for 15 years after the end of the trial so it can be available for future reference including audit.
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository. This repository is housed by the OUCRU IT and Data management group on a secure server. Electronic data will be kept for at least 20 years at OUCRU.
In line with the Wellcome and MRC Policy and Guidance on Sharing of Research Data from Population and Patient Studies, results of publicly-funded research should be freely available, manuscripts arising from the trial will, wherever possible, be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within six months of the official date of final publication. The trial will follow the OUCRU data sharing policy, which is based on a controlled access approach based on the following principles:
1. No data should be released that would compromise an ongoing trial or study.
2. There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
3. Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.
Data will be available for sharing after the primary trial publication. Researchers wishing to access data should contact the Trial Management Group in the first instance.

IPD sharing plan summary

Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version v3.3	25/07/2018	17/11/2020	No	No
Basic results		13/01/2022	13/01/2022	No	No
Results article		09/01/2023	10/01/2023	Yes	No