ISRCTN15410818 https://doi.org/10.1186/ISRCTN15410818

Investigating the impact of Maraviroc on liver inflammation in patients with HIV and fatty liver disease

Submission date
29/01/2018

Recruitment status
No longer recruiting

Registration date
12/02/2018

Overall study status
Completed

Last Edited
19/10/2022

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
Non- alcoholic fatty liver disease (NAFLD) is a common liver disease defined by fat in the liver, named as “steatosis”. NAFLD is mainly caused by metabolic disorders including obesity, hypertension, high lipids or diabetes. It is most frequently a benign disease. However, steatosis can induce liver inflammation (swelling) and scarring (fibrosis) defining non-alcoholic steatohepatitis (NASH). NASH is a more severe liver disease and is associated with a higher risk of liver complications including cirrhosis (late stage scarring) and liver cancer. HIV-infected patients are at particularly high risk of NAFLD and NASH due to drug exposure and chronic HIV infection. In non-HIV as well as HIV individuals the diagnosis of NASH requires a liver biopsy (a procedure that takes a small sample of tissue) and its best therapeutic options remain under evaluation. Maraviroc (MVC), a licensed and well-tolerated HIV drug might also have benefits on inflammation and liver fibrosis. Experimental and human studies have shown that MVC can improve liver injuries (steatosis, inflammation and fibrosis) suggesting its potential benefits in patients with NASH. No study as examined the role of MVC in HIV-associated NASH. This study aims to assess the benefits of MVC in addition to the current antiretroviral regimen of patients with HIV mono-infection and NASH.

Who can participate?
Adults aged 18-75 who have HIV and NASH.

What does the study involve?
Participants with liver-biopsy proven NASH are offered 48 weeks treatment with MVC according to standard licensed dosing. They are reviewed two weeks after treatment initiation and then every 3 months, before a liver biopsy at the end of treatment which will be compared to the pre-treatment biopsy. MVC will then be discontinued. If the study reports significant changes in liver injury after MVC treatment, we will be able to run a larger trial. This will open the way for HIV-NASH treatment which is currently not available.

What are the possible benefits and risks of participating?
There are no proven benefits to taking part, although we do hope that the care patients receive

as part of this study will reduce harmful inflammation in the liver caused by NASH. The risks include rare but potentially serious complications from the liver biopsy, and common side effects from maraviroc include postural hypotension, nausea, headaches and depression.

Where is the study run from?
This study is being run by St Mary's Hospital (UK) and takes place in hospitals in the UK.

When is the study starting and how long is it expected to run for?
June 2017 to March 2020 (as of 04/10/2018)

Who is funding the study?
VIIV Healthcare Limited (UK)

Who is the main contact?
Dr James Maurice (Scientific)

Study website
N/A

Contact information

Type(s)
Scientific

Contact name
Dr James Maurice

ORCID ID
http://orcid.org/0000-0003-1530-5328

Contact details
Liver and Antiviral Unit
10th Floor QEQM
St Mary's Hospital
South Wharf Road
London
United Kingdom
W21NY

Type(s)
Scientific

Contact name
Ms Claire Parsonage

Contact details
Hepatology Clinical Research Manager
Imperial College London
Hepatology Clinical Research Facility, Liver and Anti Viral Unit
10th Floor, QEQM Building
St Mary's Hospital

South Wharf Road
London
United Kingdom
W2 1NY
+44 (0)20 3312 6454
c.parsonage@imperial.ac.uk

Additional identifiers

EudraCT/CTIS number
2017-003172-32

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
36017

Study information

Scientific Title
Maraviroc Add-on Therapy for Steatohepatitis in HIV

Acronym
The MASH Trial

Study objectives
The aim of this study is to conduct a proof of concept trial which investigates whether Maraviroc reduces the inflammatory infiltrate in the liver of patients with HIV-NASH.

Ethics approval required
Old ethics approval format

Ethics approval(s)
East of England- Cambridge and Hertfordshire Research Ethics Committee, 30/10/2017, ref: 17 /EE/0387

Study design
Non-randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Specialty: Hepatology, Primary sub-specialty: Hepatology; UKCRC code/ Disease: Oral and Gastrointestinal/ Diseases of liver, Infection/ Human immunodeficiency virus [HIV] disease

Interventions
This is an multicentre single arm open label study. All participants have a baseline liver biopsy followed by 48 weeks treatment with Maraviroc in addition to their existing antiretroviral regimen. A second liver biopsy is performed at week 48. Participants are reviewed every 12 weeks throughout the trial, with a final follow-up review at week 52.

Intervention Type
Other

Phase
Phase II

Primary outcome measure
Change in the number of hepatic immune cells- including CD3+, CD4+, CD8+, T-bet+, CD56, CD68, CD163 and myeloperoxidase positive cells, identified using immunohistochemistry- in the liver biopsies after 48 weeks of treatment with Maraviroc as compared to baseline.

Secondary outcome measures
1. Improvement in biochemical (fasting glucose, lipids and HOMA index) metabolic parameters at 48 weeks as compared to baseline
2. Modification of circulating inflammatory cytokines, adipokines and markers of macrophage activation (high sensitive IL6, sTNFR1/2, sCD14, sCD163, hsCRP, Leptin, Total and High molecular weight adiponectin) at 48 weeks as compared to baseline
3. Number of subjects with a reduction in the NAS score by ≥2 points without worsening of fibrosis at 48 weeks as compared to baseline
4. Number of subjects with a reduction in the degree of liver steatosis, inflammation and/or ballooning at 48 weeks as compared to baseline
5. Number of subjects with a reduction of at least one stage of liver fibrosis in patients with fibrosis at 48 weeks as compared to baseline
6. Number of subjects with a reduction of Fibroscan® values and biochemical markers of fibrosis (APRI, Fib-4, NAFLD Fibrosis Score[5]) from at 48 weeks as compared to baseline
7. Number of subjects with normalization of Fibroscan values at 48 weeks
8. Number of subjects with a reduction in liver transaminases (ALT and AST) levels at 48 weeks as compared to baseline

Overall study start date
07/06/2017

Completion date
01/03/2020

Eligibility

Key inclusion criteria
1. HIV-1 infected individuals (males and females) aged 18-75 years
2. Stable antiretroviral therapy for at least one year on a regimen that is unlikely to change in the next 12 months
3. At least two consecutive undetectable HIV viral loads defined by HIV RNA ≤50 copies/mm3 for at least 6 months prior to the date of inclusion
4. CD4 count ≥ 200 cells/mm3
5. Histological evidence of NASH based on liver histology performed within 12 months prior to visit 1 (Week 0) with a NAFLD activity score (NAS) ≥ 4 with a score of at least 1 in each component (steatosis, lobular inflammation, and hepatocyte ballooning)[26] and <10% weight loss since the time of liver biopsy (see appendix 2 for criteria for offering liver biopsy)
6. Consent to second liver biopsy after 48 weeks treatment with MVC.
7. Patient able to understand and sign a consent form

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
Planned Sample Size: 30; UK Sample Size: 15

Total final enrolment
14

Key exclusion criteria
Liver co-morbidities:
1. Positive HBs antigen (HBsAg)
2. Positive HCV antibody (HCVAb), with the exception of subjects with the presence of HCVAb but negative hepatitis C virus RNA without treatment (i.e. spontaneous clearance following acute infection).
3. Underlying acute or chronic liver disease including non- B non- C viral hepatitis (A & E), autoimmune liver disease, biliary disease, hemochromatosis, Wilson´s disease, alpha-1-antitrypsin deficiency.
4. History of decompensated cirrhosis including ascites, hepatic encephalopathy, or variceal bleeding.
5. Suspicion of drug-related toxicity defined by abnormal LFTs following the recent introduction of a new medication.

Additional co-morbidities:
1. Active, serious infections that require parenteral antibiotic or antifungal therapy within 30 days prior to screening visit.
2. Active AIDS-defining disease other than oesophageal candidiasis.
3. Any active life- threatening disease
4. Active malignancy (except for early dysplastic lesions eg anal dysplasia)
5. Congestive cardiac failure
6. Platelet count < 100x103 cells/mm3 and/or INR > 1.4
7. Severe renal impairment with CrCl< 30mL/min

Lifestyle:
Excessive alcohol consumption during the last 6 months prior inclusion defined by more than 14 units/week for women or 21 units/week for men

Concomitant medications:
1. Patients actively treated with Maraviroc or having received Maraviroc over the last 12 months.
2. Weight reduction through bariatric surgery in the past 5 years or planned during the conduct of the study.
3. Current or anticipated treatment with radiation therapy, cytotoxic chemotherapeutic agents or immunomodulating agents.
4. Receiving any experimental medications within 30 days prior to screening or anticipated use during the trial.
5. Patients receiving pioglitazone, rosiglitazone, vitamin E 800 IU/day, , and/or ursodeoxycholic acid since these drugs may have confounding effect on efficacy of MVC

Others
1. Females who are pregnant or breastfeeding
2. Allergy to the study drug or its components (including peanut and soya)
3. Participation in any other clinical trial at Screening without approval from the Sponsor

Date of first enrolment
02/04/2018

Date of final enrolment
01/03/2019

Locations

Countries of recruitment
England

Germany

United Kingdom

Study participating centre
St Mary's Hospital
South Wharf Road
London

United Kingdom
W21NY

Study participating centre
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
Chelsea and Westminster Hospital
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
Centre for Infectiology
Driesener Strasse 11
Berlin
Germany
10439

Study participating centre
University Hospital
Sigmund-Freud-Strasse 25
Bonn
Germany
53127

Study participating centre
Infectiology Centre Hamburg,
Grindelallee 35
Hamburg
Germany
20146

Sponsor information

Organisation
Imperial College of Science, Technology and Medicine

Sponsor details
Imperial College London (Gisela Pereira-Barreto)
London
England
United Kingdom
SW7 2AZ

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
VIIV Healthcare Limited

Results and Publications

Publication and dissemination plan
Abstracts will be submitted to international conferences on liver diseases (EASL or AASLD) and on HIV infection (CROI). Publication of data will then be submitted to international peer-reviewed journals.

Intention to publish date
01/03/2021

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publically available repository.

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Participant information sheet	version V3	08/12/2017	12/02/2018	No	Yes
Participant information sheet	version V3	08/12/2017	12/02/2018	No	Yes
Basic results	version 4.0	05/01/2022	06/01/2022	No	No
Protocol file		14/12/2018	19/10/2022	No	No
HRA research summary			28/06/2023	No	No