Impact Objectives

- Through the use of stratified medicine, understand how factors such as viral genetics, viral load, immune parameters, host genomics and other biomarkers affect treatment of hepatitis C and the management of liver disease
- Develop clinical studies and prognostic models to predict treatment response and utilise patient information to establish the most effective and cost-effective hepatitis C treatment regimes
- Use stratified medicine technologies to predict the progression or regression of liver disease and the development of hepatocellular cancer after viral cure

Battling a silent killer

Professor Eleanor Barnes (Lead Investigator) and Dr Emma Hudson (Project Manager) *introduce the* ***STOP-HCV*** *consortium, which is working to address issues surrounding the treatment of patients with the hepatitis C virus (HCV), including high costs, retreatment requirements and the management of liver disease for those cured of HCV*

Professor Eleanor Barnes

Dr Emma Hudson

What is the Stratified Medicine to Optimise the Treatment of Patients with Hepatitis C Virus Infection (STOP-HCV) project?

In 2010, the Medical Research Council (MRC) outlined plans for its Stratified Medicine Initiative – a £60 million investment to explore the use of personalised medicine as a tool to improve the treatment and care for people living with a wide range of diseases and conditions.

In 2011, the MRC launched a call to develop and fund UK-wide research consortia, each focused on specific diseases which had an existing therapy or therapies producing different responses in patients.

Stratification could already be seen to play a role in the treatment of HCV infection and there was growing excitement in the development of new, direct-acting antivirals (DAA) with high cure rates and minimal side effects. Treatment outcome was known to be influenced by factors such as viral genotype, viral load, co-infection with other viruses, stage of liver disease and host genomics. How these factors influence one another and their effect on HCV treatment outcome and management of liver disease, are key questions the consortium aims to address in the new era of DAA therapy.

What are some of the downfalls of existing treatments for patients with HCV?

Up until five years ago, the standard of care treatment for patients with HCV was interferon plus ribavirin. This was typically a long-course of treatment (24 weeks), with unpleasant side effects, and only around a 60 per cent chance of cure.

The DAAs launched in 2012 (now in their third generation) are an all-oral treatment regime, which can be taken for shorter durations of time and have cure rates of over 95 per cent. Third generation DAAs are effective against all genotypes of HCV.

However, HCV gt3 infection (one of the predominant forms of HCV in the UK) remains more difficult to treat, especially in patients with severe liver disease.

The financial cost of the new DAAs is also an issue, and remains a controversial topic in many countries where access to treatment is limited due to costs.

Why are there still unknowns regarding patient response to hepatitis C treatment?

Currently, DAAs have the potential to successfully treat the vast majority of patients with HCV. However, some patients do fail treatment, particularly those with severe liver disease, and identifying factors contributing to this remains a focus for researchers. Resistance associated substitutions (RASs) present in the virus are likely to play a role and, by determining how these can influence treatment, we hope to optimise first-line treatment regimes, in addition to developing successful retreatment regimes for patients who have previously failed treatment. Furthermore, there is a subset of patients who would probably be cured with shorter treatment courses. One of the aims of the consortium is to use biomarkers (including host and viral genetics) to determine who can respond to shorter courses. Shortening therapy may be particularly useful when moving to treat more challenging populations, such as intravenous drug users and prison populations.

Although we are now able to cure most patients of HCV, we do not yet know if liver scarring (fibrosis) that is already established regresses after viral cure, and we do not fully understand who remains susceptible to the development of liver cancer.

What are your hopes for the future landscape of hepatitis C research?

Hepatitis is often referred to as a silent killer – people can be infected for many years without realising. One of the biggest challenges in the hepatitis field today is identifying undiagnosed patients and engaging them in effective treatment strategies that will ultimately lead to eradication of the virus.

Improving patient treatment and disease management

STOP-HCV is a consortium led by the ***University of Oxford****, UK that is exploring the use of stratified medicine for optimising treatment of patients infected with the hepatitis C virus (HCV). Its novel work is paving the way towards a brighter future for patients with HCV*

Hepatitis C is disease caused by a virus that infects the liver and, left untreated, can lead to scarring, liver failure and liver cancer. It is known as a 'silent killer' due to the fact that often, it doesn't have any noticeable symptoms and may not be found until significant liver damage has been caused. Hepatitis C virus (HCV) is usually spread through blood-to-blood contact and around 300,000 people in the UK are believed to be infected with the virus. Since the launch of direct-acting antivirals (DAAs) in 2012, around 95 per cent of patients receiving treatment are successfully cured of infection. However, drawbacks of the DAAs include cost and the prevalence of the HCV gt3 infection (a predominant form of infection in the UK), which remains difficult to treat, particularly in patients suffering from liver disease. Seeking to find new hope for patients with HCV, a consortium is exploring the use of stratified medicine, a type of personalised medicine, to treat HCV.

Stratified Medicine to Optimise the Treatment of Patients with Hepatitis C Virus Infection (STOP-HCV) is a Medical Research Council (MRC)-funded consortium led by Principal Investigator Professor Eleanor Barnes, who is based at the University of Oxford, UK. Barnes is an Honorary Consultant in Hepatology at the University, and an MRC Senior Clinical Research Fellow. In addition to leading the STOP-HCV Consortium, Barnes' research programme is focused on developing a prophylactic vaccine for HCV and a therapeutic vaccine for HBV.

A UNITED FRONT

STOP-HCV is a UK-wide consortium, with participants spanning academia and industry; 21 partner organisations and 38 consortium members who are experts in the fields of hepatitis C, genomics and big data. 'It is a national collaboration between researchers, clinicians, patient groups and industrial representatives,' explains Barnes.

Set up in 2013, through the MRC's Stratified Medicine Initiative, it explores the use of personalised medicine to improve treatment and care, and has received funding for an initial five years. Charles Gore, CEO of the Hepatitis C Trust is a key member of the consortium: 'Charles is a member of the Project Steering Committee and provides valuable advice and input, from a patient's perspective through to the development of the consortium's clinical studies and policies,' highlights Barnes. 'These insights inform the STOP-HCV work programme and ensure the ultimate goal of improving patient treatment and care remains at the forefront of the project.'

Activities are also supported by the National Institute for Health Research (NIHR) and Clinical Research Network (CRN).

A NEW STANDARD OF CARE

The driving force behind the consortium is the goal of using patient information to establish the most effective and cost-effective treatments for these patients. 'The STOP-HCV work programme integrates studies to look at host and viral genetics, immune response and biomarkers in large patient cohorts, with the aim of generating predictive models that can be used in the clinic to improve patient treatment and care,' says Barnes.

The objectives of STOP-HCV are threefold: developing prognostic models to predict treatment response and improve patient care for patients with hepatitis C; define patient strata predictive of treatment response in individuals with genotype 3 HCV infection; and define patient strata to predict the likelihood of progression towards negative clinical outcomes for those patients with liver disease.

The project is broadly divided into seven work strands (WS). WS1 includes the collection of patient samples and clinical data through an HCV biorepository (HCV Research UK: www.hcvresearchuk.org); WS2-5 involve the generation and analysis of viral and host genetic, immune phenotyping and biomarker data; WS6 concerns integration of these datasets; and WS7 focuses on establishing clinical studies and generating predictive models. The team began by laying the foundations for the consortium, recruiting patients and establishing clinical trial protocols. The next stage involved methodology quality control, with the team developing and evaluating viral and host sequencing technologies and statistical analysis tools. Currently, the researchers are gathering and analysing datasets for viral and host genetics, along with immune and biomarker studies, in order to complete the statistical analysis and integration of datasets. In the future it is hoped that models utilising these data will be made available for clinical use.

ACHIEVEMENTS TO DATE

HCV Research UK, a consortium funded by the Medical Research Foundation, underpins STOP-HCV. Together they have

> *We will be extending our statistical methods development to allow further integration of even larger and more complex datasets*

achieved great success, having established a number of patient cohorts that are beneficial to STOP-HCV and the wider research community. 'The majority of these cohorts represent patient groups who are most likely to benefit from a personalised treatment or disease management regime – in particular patients with severe liver disease,' explains Barnes. Additionally, STOP-HCV has developed methods to generate full length, deep, affordable HCV whole genome sequence (WGS) data. 'These methods allow us to assess RASs in the whole length of the viral genome and look for association with clinical outcome and disease progression,' Barnes highlights. Recognising the value of these methods, Public Health England (PHE) has implemented a project to establish them in PHE laboratories for routine clinical HCV sequencing.

In addition to these cutting-edge technologies the team has developed and is employing within the project, the researchers have created an in vitro HCV replicon system that enables them to assess the relevance of viral mutations on drug susceptibility and resistance.

A further outcome thus far is the generation of large complementary HCV WGS and host genetic datasets, and the development of new statistical tools for integration of these data. 'This has allowed us to report, for the first time, how genetic variations in the host (patient) can influence the genetic make-up of the virus,' Barnes reveals. The team's findings were recently published in *Nature Genetics*. (Ansari et al Nature Genetics 2017 Pub med ID:28394351) Barnes reveals. 'Moving forward, we will be extending our statistical methods development to allow further integration of even larger and more complex datasets.'

A BRIGHT FUTURE

Looking ahead, there are further exciting plans in the pipeline for the consortium, primarily using the toolkit they have created to: explore the role of viral resistance in relation to treatment outcome; establish effective retreatment regimes for patients who fail first-line DAA therapy; determine the long-term effects of HCV cure on liver disease; develop short-duration treatment studies in low- to middle-income countries; use stratification to expedite World Health Organization (WHO) directives to eliminate HCV by 2030. Most recently the consortium has been funded by the Wellcome Trust to begin HCV stratified studies in Hoi Chi Minh City in Vietnam (lead investigator Graham Cooke, Imperial College, London, UK).

With impressive headway already made, the STOP-HCV consortium looks set to make waves, helping improve treatment and disease management for patients with hepatitis C. Additionally, the invaluable patient cohorts the consortium is establishing, along with the data, tools and methods generated, will have a positive impact on the wider scientific research community.

Project Insights

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