Hepatitis C Infection – a Clinical Challenge Across the UK

Infections in UK
n=214,000

Increasing incidence of cirrhosis and severe liver disease

Diagnosis and treatment in Scotland (2014)
HCV Research UK

- Establish a national cohort of infected patients to promote research
- Create an infrastructure to collect and release clinical data and samples for studies on in vivo infection
- £2M funding from the Medical Research Foundation (2011)

STOP-HCV

- Derive stratification models to enhance clinical decision making
- Understand disease mechanisms that define patient strata for developing rational therapeutic approaches
- £5.2M funding from the Medical Research Council (2013)
The HCV Research UK Clinical Network

57 clinical centres

Centralised system for data and sample collection

- Blood samples
- Blood
- Data
- Clinical Database
- NHS
- Data transfer
- WWW
- Sample information
- Biorepository
- Biobank Database
Integration of the Scientific Outputs of STOP-HCV
Direct-Acting Antivirals (DAAs) – The New Era of Hepatitis C Therapy

<table>
<thead>
<tr>
<th>Protease Inhibitors</th>
<th>NS5A Inhibitors</th>
<th>Polymerase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir</td>
<td>Ledipasvir</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>Daclatasvir</td>
<td>Dasabuvir</td>
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<td>Velpatasvir</td>
<td>Elbasvir</td>
</tr>
</tbody>
</table>
Direct-Acting Antivirals (DAAs) – The New Era of Hepatitis C Therapy

How Effective are the DAAs in Real World Cohorts?

Protease Inhibitors
- NS3(pro)

NS5A Inhibitors
- NS5A
- Grazoprevir
- Ombitasvir
- Velpatasvir
- Elbasvir

Polymerase Inhibitors
- NS5B
- Simeprevir
- Ledipasvir
- Sofosbuvir
- Paritaprevir
- Daclatasvir
- Dasabuvir
- Ombitasvir
- Velpatasvir
Real World Cohorts to Assess the Outcomes of DAA Therapy

HCV Research UK Cohort (n=11,500)

EAP (n=800)

DAA Study (n=1800)

Cirrhosis Study (n=1200)

STOP-HCV1 (n=400)
Innovations in NGS - Multiplexing and Detection of Resistance Substitutions

Comparison of Next-Generation Sequencing Technologies for Comprehensive Assessment of Full-Length Hepatitis C Viral Genomes

Emma Thomson, a Camilla L. C. Ip, b Anjna Badhan, b Mette T. Christiansen, a Walt Adamson, a M. Azim Ansari, a, b David Bibby, d
Judith Breuer, a Anthony Brown, c Rory Bowden, c Josie Bryant, c David Bonsall, e Ana Da Silva Filipe, e Chris Hinds, e Emma Hudson, e
Paul Klenerman, a Kieren Lythgow, f Jean L. Mbisa, a John McLaughlan, a Richard Myers, d Paolo Piazza, a Sunando Roy, a Amy Trebes, b
Vattipally B. Sreenu, a Jeroen Witteveen, f STOP-HCV Consortium, Eleanor Barnes, e Peter Simmonds, e, f
HCV-GLUE for Rapid Genotyping and Detection of Resistance Substitutions

Submit your sequence files in FASTA nucleotide format for automated analysis of the sequence type and interpretation of the nucleotide content.

<table>
<thead>
<tr>
<th>File</th>
<th>Size</th>
<th>Variation categories</th>
<th>Status</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA44_1-Ref.1a.x.x.LTD62XF224.AF511950.fasta</td>
<td>0.01 MB</td>
<td>Resistance-associated variants</td>
<td>✔️</td>
<td>![Show analysis] ![Remove]</td>
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Analysis Results

<table>
<thead>
<tr>
<th>Typing summary</th>
<th>Variation summary</th>
<th>Genome detail</th>
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<tbody>
<tr>
<td>File</td>
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<td>Variation category</td>
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<td>AA44_1-Ref.1a.x.x.LTD62XF224.AF511950.fasta</td>
<td>AA44_1-Ref.1a.x.x.LTD62XF224.AF511950.sam S208</td>
<td>Resistance-associated variants</td>
</tr>
</tbody>
</table>

Resistance-associated variants where a match was found in the query sequence: 4

<table>
<thead>
<tr>
<th>Reference sequence</th>
<th>Genome feature</th>
<th>Resistance-associated variants</th>
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<tbody>
<tr>
<td>H77_AF009606</td>
<td>NS3</td>
<td>NS3:175L</td>
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<tr>
<td>H77_AF009606</td>
<td>NS5A</td>
<td>NS5A:28M NS5A:3DQ NS5A:311</td>
</tr>
</tbody>
</table>
The DAA Experience with the Expanded Access Programme

- HCV gt3 responds less well to therapy
- About 3% of patients misdiagnosed for viral genotype
- Genotype switching between pre- and post-therapy for some relapsers
- Rare subtypes respond less well to therapy
Does Cure of Infection Affect Liver Disease Prognosis?

Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy

Unexpected high incidence of hepatocellular carcinoma in cirrhotic patients with sustained virologic response following interferon-free direct-acting antiviral treatment

Unexpected high incidence of hepatocellular carcinoma in patients with hepatitis C in the era of DAAs: Too alarming?
Long-term Outcomes – The Longitudinal Cirrhosis Study

Cohort established (n=1264)
Data and samples
Data and samples
Data and samples
Data and samples

- Extensive host genotyping
- Viral sequences for all patients
- Responses to therapy
- Identify and validate markers for HCC
What about the Future?

STOP-HBV
With thanks to...