Non-A, Non-B hepatitis and normalization of ALT to hepatitis C virus and eradication

Posttransfusion Hepatitis After Exclusion of Commercial and Hepatitis-B Antigen-Positive Donors

Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome
QUI-LIMahoo, GEORGE Kuo, AMY J. WEiner, LACY R. OVERBY, DANIEL W. BRADLEY, MICHAEL Houghton

TREATMENT OF CHRONIC NON-A, NON-B HEPATITIS WITH RECOMBINANT HUMAN ALPHA INTERFERON
A Preliminary Report
JAY H. HOOFNAGLE, M.D., KEVIN D. MULLEN, M.D., D. BRIAN JONES, M.D., VINOD RUSTGI, M.D., ADRIAN DI BISCAGLIE, M.D., MARION PETERS, M.D., JEANNE G. WAGGONER, B.A., YOON PARK, R.N., and E. ANTHONY JONES, M.D.

A random-primed complementary DNA library was constructed from plasma containing the uncharacterized non-A, non-B hepatitis (NANBH) agent and screened with serum from a patient diagnosed with NANBH. A complementary DNA clone was isolated that was shown to encode an antigen associated specifically with NANBH infections. This clone is not derived from host DNA but from an RNA molecule present in NANBH infections that consists of at least 10,000 nucleotides and that is positive-stranded with respect to the encoded NANBH antigen. These data indicate that this clone is derived from the genome of the NANBH agent and are consistent with the agent being similar to the togaviridae or flaviridae. This molecular approach should be of great value in the isolation and characterization of other unidentified infectious agents.

Alter Annals of Internal Medicine 1972
Hoofnagle NEJM 1986
Choo QL Science 1989
Chronic HCV infection is common and heterogeneous

Prevalence (Viremic)
- 0.0%-0.6%
- 0.6%-0.8%
- 0.8%-1.3%
- 1.3%-2.9%
- 2.9%-7.8%

Total Infected (Viremic)
- 200K-650K
- 650K-1.9M
- 0-200K
- 1.9M-3.5M
- 3.5M-9.2M

HCV life cycle presents multiple antiviral targets

1. Entry
2. Endosomal release and IRES dependent translation
3. Protease cleavages
4. Membranous web formation
5. NS5B RNA dependent polymerase (RdRp)
6. Lipoprotein assembly linked to NS5A
7. Cellular targets

Adapted by David Thomas for Ray Fields Virology
NS3/4A protease inhibitor

Rapid and potent HCV suppression with BILN2061 (2003)

Selection of telaprevir-resistant variants with monotherapy x 14 days

Lamarre Nature 2003
Kieffer Hepatology 2007
HCV Drug Development Advisory Group
NS5A inhibitors

Rapid and potent antiviral activity with a single dose of daclatasvir (2010)

Selection of daclatasvir-resistant variants with monotherapy x 14 days

Gao Nature 2010
Nettles Hepatology 2011
HCV Drug Development Advisory Group;
NS5B polymerase (non-nucleoside) inhibitors

Binding sites for non-nucleoside HCV NS5B polymerase inhibitors

HCV RNA suppression over 3 days with dasabuvir (ABT-333) monotherapy (~1 log_{10})

Poordad EASL 2012
NS5B (nucleos(t)ide analogue) polymerase inhibitors

Highly conserved, NS5B active site

Potent HCV suppression with sofosbuvir alone, (2010)

Sofosbuvir, β-d-2'-deoxy-2'-α-fluoro-2'-β-C-methyluridine nucleotide prodrug (2010)

Sofia J Med Chem 2010
Gane NEJM 2013
HCV Drug Development Advisory Group
Ribavirin prevents the emergence of drug-resistant variants

High rate of HCV breakthrough with telaprevir without ribavirin

Zeuzem S et al. Hepatology 2012
Host-targeting HCV inhibitors

Miravirsen — antisense oligonucleotide that sequesters mature miR-122

Alisporivir — blocks the isomerase activity cyclophilin A

Janssen New Eng Journal Med 2013
Gallay Drug Des Devel Ther. 2013
## Combination antiviral therapy

*Interferon is not recommended (2015)*

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>NS3</th>
<th>NS5A</th>
<th>Non-nuc NS5B</th>
<th>Nuc NS5B</th>
<th>RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir + dasabuvir</td>
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<tr>
<td>Asunaprevir/daclatasvir/beclabuvir FDC</td>
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<td>1a</td>
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<tr>
<td>Grazoprevir/elbasvir FDC</td>
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<tr>
<td>Sofosbuvir/ledipasvir FDC</td>
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<tr>
<td>Sofosbuvir + daclatasvir</td>
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<tr>
<td>Sofosbuvir + simeprevir</td>
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<tr>
<td>MK3682/elbasvir/grazoprevir FDC</td>
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<tr>
<td>Sofosbuvir/ledipasvir/GS9857 FDC</td>
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</tbody>
</table>
Treatment of persons with HCV genotype 1a or 1b infection

DAA regimens that do not include a nucleos(t)ide polymerase inhibitor
Daclatasvir + asunaprevir (NS5A + NS3)
First report of interferon-free cure (2012)

Lok NEJM 2012
McPhee Hepatology 2013
Paritaprevir/r + dasabuvir + ribavirin in patients (NS3 + non-nuc NS5B)

Poor response in patients with prior non-response to interferon

Patient with prior null-response (< 2 log_{10} decline) during treatment with peginterferon/ribavirin

U = undetectable (HCV RNA not detected)

Poordad NEJM 2013
HCV cure with variable combinations of paritaprevir/r + ombitasvir + dasabuvir + ribavirin (NS3 ± NS5A ± non-nuc NS5B ± ribavirin)

<table>
<thead>
<tr>
<th>No Ombitasvir (NS5A inhibitor)</th>
<th>No Dasabuvir (Non-nucleoside NS5B inhibitor)</th>
<th>No Ribavirin</th>
<th>Three DAAs + Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR (%)</td>
<td>SVR (%)</td>
<td>SVR (%)</td>
<td>SVR (%)</td>
</tr>
<tr>
<td>83 N=41</td>
<td>89 N=79</td>
<td>89 N=79</td>
<td>96 N=79</td>
</tr>
<tr>
<td>Viral Failure (%)</td>
<td>Viral Failure (%)</td>
<td>Viral Failure (%)</td>
<td>Viral Failure (%)</td>
</tr>
<tr>
<td>12.2</td>
<td>10.1</td>
<td>7.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Kowdley NJEM 2014
High SVR rate with three DAAs (plus ribavirin for genotype 1a)

Ombitasvir/paritaprevir + dasabuvir with or without ribavirin

Genotype 1b
1 patient with breakthrough*

Genotype 1a – no ribavirin
16 patients with virologic failure (6 breakthrough and 10 relapse)*

Genotype 1a – ribavirin
2 patients with virologic failure (1 breakthrough and 1 relapse)*

*Variants in patients with virologic failure:
NS3, D168V
NS5A, M28T and Q30R
NS5B, S556G

HCV cure may take longer in patients with cirrhosis and prior nonresponse to interferon

HCV relapse rate: 12 week group [12 of 203 patients, for a rate of 5.9% (95% CI, 2.7 to 9.2)] vs 24 week group [1 of 164 patients, for a rate of 0.6% (95% CI, 0 to 1.8)]
HCV eradication with the fixed-dose combination of daclatasvir/asunaprevir)/beclabuvir (plus ribavirin for genotype 1a)

Patients with cirrhosis + no prior therapy

Patients with cirrhosis + prior therapy

## Grazoprevir + elbasvir (NS3 + NS5A)

### SVR12 (%), 95% CI

<table>
<thead>
<tr>
<th>Treatment duration (weeks)</th>
<th>Previously untreated patients with cirrhosis</th>
<th>PR-null with or without cirrhosis</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Ribavirin (arm B4)</td>
<td>No ribavirin (arm B5)</td>
<td>Ribavirin (arm B8)</td>
</tr>
<tr>
<td>SVR12 (95% CI)</td>
<td>28/31, 90% (74-98)</td>
<td>28/29, 97% (82-100)</td>
<td>31/32, 97% (84-100)</td>
</tr>
<tr>
<td>Lost to follow-up or discontinued early due to reasons other than virological failure</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Virological at breakthrough</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Virological relapse</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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Lawitz Lancet 2014
Treatment of Persons with HCV Genotype 1a or 1b Infection

DAA regimens that include a nucleos(t)ide polymerase inhibitor
Development of nucleos(t)ide analogue NS5B polymerase inhibitors has been arduous

- HCV suppression with an uridine nucleotide polymerase inhibitor prodrug, MK-3682 (formerly IDX21437)
  - In Phase 2 trials

- Cardiac dysfunction associated BMS-986094, guanosine nucleotide polymerase inhibitor
  - Discontinued
HCV eradication with the combination of inhibitors of NS5A or NS3 plus nuc NS5B polymerase

Daclatasvir plus Sofosbuvir ± Ribavirin

Simeprevir (NS3) plus Sofosbuvir ± Ribavirin

Sustained Virologic Response = 98%

Sułkowski  NEJM 2014
Lawitz  Lancet 2014
Ledipasvir/sofosbuvir (NS5A/nuc NS5B) fixed-dose combination – no ribavirin

Persons with no prior HCV treatment

8 weeks
20 patients with relapse, 4.6%
HCV RNA < 6 million IU/mL, only 2%

12 weeks
4 patients with relapse, 0.6%

24 weeks
1 patient with relapse, 0.2%

*Variants in patients with virologic failure:
NS5A, L31V/M/I, Y93H, Q30R
NS5B, None

HCV eradication may take longer or require ribavirin in persons with cirrhosis and prior nonresponse to interferon.

Integrated analysis of patients with cirrhosis (n = 513)

<table>
<thead>
<tr>
<th>SVR by treatment regimen</th>
<th>Treatment naive</th>
<th>Treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall SVR</td>
<td>98%</td>
<td>95%</td>
</tr>
<tr>
<td>Duration (12 or 24) ± RBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDV/SOF 12 weeks</td>
<td>96%</td>
<td>90%</td>
</tr>
<tr>
<td>LDV/SOF + RBV 12 wks</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>LDV/SOF 24 weeks</td>
<td>97%</td>
<td>98%</td>
</tr>
<tr>
<td>LDV/SOF + RBV 24 wks</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Bourlière Lancet 2015
Next steps for treatment of HCV genotype 1 infection—Short duration of therapy?

6 weeks of Sofosbuvir/ledipasvir + GS-9669 or GS-9451 (nuc NS5B/NS5A + non-nuc NS5B or NS3)

4, 6 or 8 weeks of grazoprevir/elbasvir + sofosbuvir, persons with and without cirrhosis

Kohli Lancet 2015
Lawitz AASLD 2014
Treatment of persons with HCV genotype 2, 3, 4, 5, or 6 infection
Genotype distribution according to low, middle, or high regional income regions

Razavi H et al. The Liver Meeting 2013; Abstract 2233; Ruane PJ et al. The Liver Meeting 2013; Abstract 1090*
NS3 inhibitor simeprevir is active in patients with HCV genotype 1, 2, 4, 5, and 6, but not 3.
FISSION: PegIFN/RBV vs sofosbuvir + RBV for GT 2/3

Sofosbuvir + ribavirin or daclatasvir for treatment of persons with HCV genotype 3 infection

Sofosbuvir + ribavirin for 24 weeks in persons with HCV genotype 2 or 3 infection

Daclatasvir + sofosbuvir for 12 weeks in persons with HIV infection and HCV genotype 1, 2, 3, or 4 infection

Daclatasvir + sofosbuvir for 12 weeks in persons with HCV genotype 3 infection

Zeuzem NEJM 2014;
Wyles CROI 2015
Nelson Hepatology 2015
Multiple, oral HCV antiviral regimens are effective for persons infected with genotype 4.

- **Ombitasvir/Paritaprevir/r**
  - SVR in 19 of 20 patients treated at the NIH/NIAID.
  - **Sofosbuvir/ledipasvir FDC** – SVR in 19 of 19 patients treated.
  - **Daclatasvir/asunaprevir/beclabuvir** – SVR in 19 of 19 patients treated.

Simeprevir monotherapy has potent antiviral activity against genotype 4.

Kapoor AASLD 2014; Pol AASLD 2014; Hassanenein J Hepatol 2015; Esmat AASLD 2014; Lenz J Hepatol 2013
Genotypes 1, 2, 3, 4, 5, and 6 – with the combination of sofosbuvir/velpatasvir (nuc NS5B/NS5A) +/- GS-9857

Recruiting

**Safety and Efficacy of GS-9857 Plus Sofosbuvir/GS-5816 Fixed Dose Combination in Adults With Chronic Genotype 1 HCV Infection**

- **Condition:** Hepatitis C Virus Infection
- **Interventions:** Drug: GS-9857; Drug: SOF/GS-5816

Recruiting

**Safety and Efficacy of GS-9857 Plus Sofosbuvir/GS-5816 Fixed Dose Combination in Adults With Chronic Non-Genotype 1 HCV Infection**

- **Condition:** Hepatitis C Virus Infection
- **Interventions:** Drug: GS-9857; Drug: SOF/GS-5816

Everson EASL 2014
Recommendations for Testing, Managing, and Treating Hepatitis C

This website is constantly being updated. Please remember to always refresh your page.

Background of the Hepatitis C Guidance

New direct-acting oral agents capable of curing hepatitis C virus (HCV) infection have been approved for use in the United States. The initial direct-acting agents were approved in 2011, and many more oral drugs are expected to be approved in the next few years. As new information is presented at scientific conferences and published in peer-reviewed journals, health care practitioners have expressed a need for a credible source of unbiased guidance on how best to treat their patients with HCV infection. To provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management.

New sections will be added, and the recommendations will be updated on a regular basis as new information becomes available. An ongoing summary of “recent changes” will also be available for readers who want to be directed to updates and changes.

About Hepatitis C

An estimated 3 million to 4 million persons in the United States are chronically infected with HCV, and approximately half are unaware of their status. These individuals may ultimately progress to advanced liver disease and/or hepatocellular cancer. However, these outcomes can be prevented by treatment, which is rapidly improving and offers the potential of a cure to more patients than has been previously possible.