Treatment of Chronic HCV Genotype 4

Robert G. Gish MD
Staff Physician, (Consultant) Stanford University Medical Center
Senior Medical Director, St Josephs Hospital and Medical Center, Liver Program, Phoenix, Arizona
Clinical Professor (Adjunct) of Medicine, University of Nevada, Las Vegas
Medical Director, Hepatitis B Foundation
Vice Chair, Executive Committee, National Viral Hepatitis Roundtable (NVHR)

Last Updated: October 19, 2015
Treatment of Chronic HCV Genotype 4

- Background and Definitions
- Initial Treatment and Retreatment of Prior Relapsers
- Retreatment of Prior Nonresponders
- Issues and Controversies
- Future Therapies
- Summary
TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 4

Background and Definitions
Treatment of Chronic HCV Genotype 4

Background

- HCV infects ~ 5 million people in the US today
- Genotype 4 accounts for about 1-2% of HCV infections in US
- Genotype 4 very important in Egypt, Saudi Arabia, North Africa, and Southern Europe and immigrants from these regions
- Approximately 70% of patients with genotype 4 HCV have moderate to severe steatosis with or without sinusoidal fibrosis (similar to GT3)
- Historic SVR rates with IFN-based therapy between GT1 and GT 2,3
TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 4

Initial Treatment
### Genotype 4 HCV: Initial Treatment

<table>
<thead>
<tr>
<th>Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir-Sofosbuvir x 12 weeks</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir + Ribavirin x 12 weeks</td>
</tr>
<tr>
<td>Sofosbuvir + Ribavirin x 24 weeks</td>
</tr>
</tbody>
</table>

**Alternative Regimen, Patients Eligible to Receive Interferon**

| Sofosbuvir + Ribavirin + Peginterferon x 12 weeks |

Source: AASLD/IDSA/IAS-USA (www.hcvguidelines.org).
Treatment-Naïve & Prior Relapsers with GT4 Chronic HCV

Key Studies that Support Treatment Recommendations

- **Ledipasvir-Sofosbuvir**
  - NIAID Synergy (Genotype 4)

- **Ombitasvir-Paritaprevir-Ritonavir**
  - PEARL-I

- **Sofosbuvir + Ribavirin**
  - Egyptian Ancestry

- **Sofosbuvir + Ribavirin + Peginterferon**
  - NEUTRINO
Ledipasvir-Sofosbuvir in Genotype 4 NIAID SYNERGY (GT4) Trial: Features

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
</table>

Genotype 4
Treatment Naïve (n = 13)
Treatment Experienced (n = 8)

n = 21

Ledipasvir-Sofosbuvir

SVR12

Drug Dosing
Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

Ledipasvir-Sofosbuvir in Genotype 4 NIAID SYNERGY (GT4) Trial: Results

NIH SYNERGY: SVR 12, Intent to Treat Analysis

Ledipasvir-Sofosbuvir Treated Patients

![Bar chart showing the percentage of patients with HCV RNA < 43 IU/ml after treatment. The graph shows that 95% of all treated patients achieved the desired outcome, 92% of treatment-naive patients achieved the desired outcome, and 100% of treatment-experienced patients achieved the desired outcome. One patient did not complete the treatment due to non-adherence.]

*1 patient did not complete 12 weeks of treatment due to drug non-adherence

Ombitasvir + Paritaprevir + Ritonavir +/- RBV in HCV GT4
PEARL-I: Regimens

**HCV Treatment Naïve GT4**

- **n = 44**
  - Ombitasvir + Paritaprevir + Ritonavir
  - SVR12

- **n = 42**
  - Ombitasvir + Paritaprevir + Ritonavir + Ribavirin
  - SVR12

**HCV Treatment Experienced GT4**

- **n = 49**
  - Ombitasvir + Paritaprevir + Ritonavir + Ribavirin
  - SVR12

**Drug Dosing**
Ombitasvir (25 mg once daily), Paritaprevir (150 mg once daily), Ritonavir (100 mg once daily)
Ribavirin (RBV): weight-based and divided bid (1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg)

Ombitasvir + Paritaprevir + Ritonavir +/- RBV in HCV GT4
PEARL-I: Results

PEARL-I: SVR 12 Rates (HCV RNA <25 IU/mL)

Patients (%) with SVR 12

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR 12 Rates (HCV RNA &lt;25 IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBV/PTV/r</td>
<td>40/44</td>
</tr>
<tr>
<td>OBV/PTV/r + RBV</td>
<td>42/42</td>
</tr>
<tr>
<td>OBV/PTV/r + RBV</td>
<td>49/49</td>
</tr>
</tbody>
</table>

Treatment-Naive

Treatment-Experienced

OBV/PTV/r = Ombitasvir-Paritaprevir-Ritonavir; RBV = ribavirin

Sofosbuvir and Ribavirin in HCV Genotype 4 Egyptian Ancestry Trial: Design

**Drug Dosing**
- Sofosbuvir: 400 mg once daily
- Weight-Based Ribavirin (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Sofosbuvir and Ribavirin in HCV Genotype 4 Egyptian Ancestry Trial: Results

SVR 12 by Regimen Duration and Treatment Experience

<table>
<thead>
<tr>
<th>Treatment Experience</th>
<th>SOF + RBV x 12 weeks</th>
<th>SOF + RBV x 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Naive</td>
<td>11/14 (79%)</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Treatment Experienced</td>
<td>10/17 (59%)</td>
<td>13/15 (87%)</td>
</tr>
</tbody>
</table>

Sofosbuvir + PEG + RBV: Treatment-Naive HCV GT 1,4,5,6

NEUTRINO Trial: Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N = 327 (N = 28 for GT 4)</td>
<td>Sofosbuvir + PEG + RBV</td>
<td>SVR12</td>
<td></td>
</tr>
</tbody>
</table>

Drug Dosing
Sofosbuvir: 400 mg once daily
Peginterferon alfa-2a: 180 µg once weekly
Ribavirin (weight-based and in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Sofosbuvir + PEG + RBV: Treatment-Naive HCV GT 1,4,5,6
NEUTRINO Trial: Results

NEUTRINO: SVR 12 by Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients with SVR 12 (%)</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1</td>
<td>89</td>
<td>261/292</td>
</tr>
<tr>
<td>GT 4</td>
<td>96</td>
<td>27/28</td>
</tr>
<tr>
<td>GT 5,6</td>
<td>100</td>
<td>7/7</td>
</tr>
</tbody>
</table>

GT = genotype

Retreatment of Persons in Whom Prior Therapy Failed
## Genotype 4 HCV: Retreatment, Prior Failure with Peginterferon + Ribavirin

<table>
<thead>
<tr>
<th>Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir-Sofosbuvir x 12 weeks</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir + Ribavirin x 12 weeks</td>
</tr>
<tr>
<td>Sofosbuvir + Ribavirin + Peginterferon x 12 weeks</td>
</tr>
<tr>
<td>Sofosbuvir + Ribavirin x 24 weeks</td>
</tr>
</tbody>
</table>
Retreatment of GT4 Chronic HCV

Key Studies that Support Treatment Recommendations

• Ledipasvir-Sofosbuvir
  - NIAID Synergy (Genotype 4)

• Ombitasvir-Paritaprevir-Ritonavir
  - PEARL-I

• Sofosbuvir + Ribavirin + Peginterferon
  - NEUTRINO (data for treatment-naïve patients)

• Sofosbuvir + Ribavirin
  - Egyptian Ancestry
Ledipasvir-Sofosbuvir in Genotype 4 NIAID SYNERGY (GT4) Trial: Results

NIH SYNERGY: SVR 12, Intent to Treat Analysis

- **All**: 95% (20/21) of treated patients had HCV RNA < 43 IU/ml
- **Treatment-Naïve**: 92% (12/13) of treated patients had HCV RNA < 43 IU/ml
- **Treatment-Experienced**: 100% (8/8) of treated patients had HCV RNA < 43 IU/ml

*1 patient did not complete 12 weeks of treatment due to drug non-adherence

Ombitasvir + Paritaprevir + Ritonavir +/- RBV in HCV GT4
PEARL-I: Results

PEARL-I: SVR 12 Rates (HCV RNA <25 IU/mL)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment-Naive</th>
<th>Treatment-Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBV/PTV/r</td>
<td>40/44</td>
<td>42/42</td>
</tr>
<tr>
<td>OBV/PTV/r + RBV</td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>OBV/PTV/r + RBV</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

OBV/PTV/r = Ombitasvir-Paritaprevir-Ritonavir; RBV = ribavirin

Sofosbuvir and Ribavirin in HCV Genotype 4 Egyptian Ancestry Trial: Results

SVR 12 by Regimen Duration and Treatment Experience

<table>
<thead>
<tr>
<th>Treatment Experience</th>
<th>Regimen Duration</th>
<th>Patients with SVR 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Naive</td>
<td>SOF + RBV x 12 weeks</td>
<td>11/14 (79%)</td>
</tr>
<tr>
<td></td>
<td>SOF + RBV x 24 weeks</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Treatment Experienced</td>
<td>SOF + RBV x 12 weeks</td>
<td>10/17 (59%)</td>
</tr>
<tr>
<td></td>
<td>SOF + RBV x 24 weeks</td>
<td>13/15 (87%)</td>
</tr>
</tbody>
</table>

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 4

Issues and Controversies
Issues and Controversies

• Cost of Therapy
  ❖ What is real cost?
  ❖ Cost per cure?
  ❖ Discounts

• When to Defer or Decline Therapy
  ❖ Decisions on when to warehouse if any?
  ❖ Noncompliance
  ❖ Short life span

• (Non) Role of IL-28b Testing

• Is the Degree of Liver Fibrosis useful to allocate treatment
  ❖ How to stage?
How is cost of therapy impacting treatment decisions?
## Estimated Medication Cost for Treatment of Genotype 4 Chronic HCV

<table>
<thead>
<tr>
<th>Regimen and Duration</th>
<th>AWAC Regimen Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir-Sofosbuvir x 12 weeks</td>
<td>$94,500</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir + Ribavirin x 12 weeks</td>
<td>$77,000</td>
</tr>
<tr>
<td>Sofosbuvir + Ribavirin x 24 weeks</td>
<td>$169,000</td>
</tr>
<tr>
<td>Sofosbuvir + Ribavirin + Peginterferon x 12 weeks</td>
<td>$97,000</td>
</tr>
</tbody>
</table>

**AWAC =** Average Wholesale Acquisition Cost

*Note: health care systems may receive substantial discounts*
Should one decline or defer therapy?
Factors Favoring Treat Now for all GT4

- Advanced Fibrosis (F3-F4)
  - Platelet count < 150,000/uL
  - Large spleen and/or portal vein (Over 12 rule = Spleen > 12 cm or PV > 12 mm)
  - Esophageal varices

- Synthetic dysfunction, low albumin, high INR

- Systemic disease
  - Cryoglobulinemia (+RhF)

- Highly motivated patients/symptoms

- Patients with Increased Mortality Risk
  - All cause
  - HCC risk
Hepatitis C: Genotype 4

Future Treatment Options
Future Regimens for GT-4

• **Daclatasvir + Sofosbuvir**
  - Daclatasvir: NS5A replication inhibitor
  - Sofosbuvir: NS5B polymerase inhibitor

• **Sofosbuvir-Velpatasvir (GS-5816) Once Daily Fixed-Dose Combination**
  - Velpatasvir: NS5A replication inhibitor, second generation, pangenotypic
  - Sofosbuvir: NS5B polymerase inhibitor
  ✧ ASTRAL-1 Study\(^1\): 116/116 (100%) with GT4 achieved SVR12

• **Grazoprevir-Elbasvir Once Daily Fixed-Dose Combination:**
  - Grazoprevir: NS3/4A protease inhibitor
  - Elbasvir: NS5A replication inhibitor
  ✧ C-EDGE Study\(^2\): 16/16 (100%) with GT4 achieved SVR12

\(^1\)Gilead Sciences
Summary Points for Treatment of Chronic HCV GT-4

- HCV GT4 uncommon in US, but prevalent in Egypt, Saudi Arabia, North African, and southern Europe as well as immigrants from these regions to the US including Coptic population and horn of Africa (Sudan, Ethiopia, Somalia and Eritrea)

- For initial treatment of GT4 the recommended regimens are:
  - Ledipasvir-sofosbuvir x 12 weeks
  - Ombitasvir-paritaprevir-ritonavir + Ribavirin x 12 weeks
  - Sofosbuvir + Ribavirin x 24 weeks

- For retreatment of patients with GT4, the recommended regimens are the same as initial treatment with one additional regimen included:
  - Sofosbuvir + Ribavirin + Peginterferon x 12 weeks
This slide deck is from the University of Washington’s *Hepatitis C Online* and *Hepatitis Web Study* projects.

**Hepatitis C Online**
www.hepatitisc.uw.edu

**Hepatitis Web Study**
http://depts.washington.edu/hepstudy/

Funded by a grant from the Centers for Disease Control and Prevention.