Treatment of Chronic HCV Genotype 5 or 6

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Treatment of Chronic HCV Genotype 5 or 6

- 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 5 OR 6

Background and Definitions
Hepatitis C Genotype 5 or 6

Background

- HCV infects ~ 5 million people in the US today
- Fewer than 2% of HCV infections in US caused by GT 5 or 6
- GT5 infection endemic in South Africa and very rare in US
- GT6 important in Vietnam, SE China, and other countries in Southeast Asia
- Historically SVR rates for GT 5,6 with PEG-based therapy between GT1 and GT 2,3
Virologic Responses with HCV Therapy
Relapser and Nonresponder (Null and Partial)

Different Types of Virologic Failure with HCV Therapy

- **Null Responder**
- **Partial Responder**
- **Relapser**

**HCV RNA IU/ml**

**Treatment Week**

- Undetectable
### Criteria for Interferon Ineligible

Interferon Ineligible is defined as one or more of the following:

- Intolerance to interferon
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to peginterferon or any of its components
- Decompensated hepatic disease
- Major uncontrolled depressive illness
- A baseline neutrophil count below 1500/µL, a baseline platelet count below 90,000/µL or baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 5 OR 6
Treatment-Naïve and Prior Relapsers
### AASLD/IDSA/IAS-USA 2014 HCV Treatment Recommendations

**Initial Therapy for Patients with Genotype 5 or 6 Chronic HCV**

<table>
<thead>
<tr>
<th>Patients with GT 5 or 6 HCV: Initial Treatment &amp; Retreatment of Relapsers*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended Therapy, Interferon Eligible</strong></td>
</tr>
<tr>
<td>Sofosbuvir + Peginterferon + Ribavirin x 12 weeks</td>
</tr>
<tr>
<td><strong>Alternative Therapy, Interferon Eligible</strong></td>
</tr>
<tr>
<td>Peginterferon + Ribavirin x 48 weeks</td>
</tr>
<tr>
<td><strong>Not Recommended</strong></td>
</tr>
<tr>
<td>Monotherapy with Peginterferon, Ribavirin, or a Direct Acting Antiviral Agent</td>
</tr>
<tr>
<td>Telaprevir- or Boceprevir-based Regimens</td>
</tr>
</tbody>
</table>

*Patients previously treated with peginterferon plus ribavirin and had relapse*
Treatment-Naïve & Prior Relapsers with GT 5 or 6 Chronic HCV
Key Studies that Support Treatment Recommendations

• Sofosbuvir + Peginterferon + Ribavirin
  - NEUTRINO
  - ATOMIC
## NEUTRINO Trial: Features

- **Design**: Single-arm, open-label, phase 3 trial of triple therapy with sofosbuvir + peginterferon + ribavirin in HCV genotypes 1, 4, 5, or 6

- **Setting**: 56 sites in United States, enrolled June-August 2012

- **Entry Criteria**
  - Treatment-naïve, chronic HCV monoinfection
  - HCV RNA $\geq 10,000$ IU/ml
  - HCV Genotypes 1, 4, 5, or 6

- **Primary End-Point**: SVR12
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>
</table>

N = 327

Sofosbuvir + PEG + RBV

SVR12

**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

GT 1: 261/292 (89%)
GT 4: 27/28 (96%)
GT 5,6: 7/7 (100%)

GT = genotype

Sofosbuvir + Peginterferon + Ribavirin in Genotypes 1, 4, 5, 6

ATOMIC Trial: Study Overview

<table>
<thead>
<tr>
<th>ATOMIC Trial: Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong>: Randomized, open-label, phase 2 trial investigating effectiveness and required duration of sofosbuvir, peginterferon, and ribavirin in treatment-naïve patients with GT 1, 4, 5, or 6</td>
</tr>
<tr>
<td><strong>Setting</strong>: 42 centers in United States and Puerto Rico</td>
</tr>
<tr>
<td><strong>Entry Criteria</strong></td>
</tr>
<tr>
<td>- Chronic HCV infection with HCV genotype 1, 4, 5, or 6</td>
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<tr>
<td>- Treatment-naïve</td>
</tr>
<tr>
<td>- Age 18 or older</td>
</tr>
<tr>
<td>- HCV RNA ≥ 50,000 IU/mL</td>
</tr>
<tr>
<td>- Absence of cirrhosis</td>
</tr>
<tr>
<td>- Absence of coinfection with HBV or HIV</td>
</tr>
<tr>
<td>- BMI ≤ 18 kg/m²</td>
</tr>
<tr>
<td><strong>Primary End-Point</strong>: SVR24</td>
</tr>
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Sofosbuvir + Peginterferon + Ribavirin in Genotypes 1,4,5,6

ATOMIC Trial: Design

Week 0 12 24 36 48

Cohort A
n = 52
GT 1
GT4
GT5
GT6

SOF + PEG + RBV

SVR24

Cohort B
n = 125

SOF + PEG + RBV

SVR24

Cohort C
n = 155

SOF + PEG + RBV
SOF
SOF + RBV

SVR24

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

Sofosbuvir + Peginterferon + Ribavirin in Genotypes 1, 4, 5, 6

ATOMIC Trial: Results, by Cohort (Regimen)

ATOMIC: SVR 24 by Cohort (Regimen)

Patients (%) with SVR24

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patients with Genotype 1, 4, or 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A</td>
<td>46/52</td>
</tr>
<tr>
<td>Cohort B</td>
<td>97/109</td>
</tr>
<tr>
<td>Cohort C</td>
<td>135/155</td>
</tr>
</tbody>
</table>

Sofosbuvir + Peginterferon + Ribavirin in Genotypes 1, 4, 5, 6
ATOMIC Trial: Results, by Cohort (Regimen)

ATOMIC: SVR 24 by Genotype

Notes: (1) No patients with Genotype 5 enrolled in study
(2) All patients with Genotype 4 or 6 received 24 weeks of SOF + PEG + RBV
(3) The 2 patients with Genotype 4 and failure resulted from lost to follow-up at end of treatment

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 5 OR 6
Retreatment of Prior Nonresponders
### AASLD/IDSA/IAS-USA 2014 HCV Treatment Recommendations
#### Retreatment of Patients with Genotype 5 or 6 Chronic HCV

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<tr>
<td><strong>Recommended Therapy^</strong></td>
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<td>Sofosbuvir + Peginterferon + Ribavirin x 12 weeks</td>
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<td><strong>Alternative Therapy</strong></td>
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<td>None</td>
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<tr>
<td>Peginterferon + Ribavirin +/- [Boceprevir or Simeprevir or Telaprevir]</td>
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<tr>
<td>Treatment of Decompensated Cirrhosis with Peginterferon</td>
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</table>

^Expert consultation is recommended to determine the optimal duration of therapy
*Patients who experienced nonresponse (partial or null) with Peginterferon plus Ribavirin therapy

Lack of Retreatment Studies

- Sparse retreatment data for patients with genotypes 5 and 6
- EMEA has approved SOF for Genotype 5 and 6 from this limited treatment data
- US FDA has not included Genotype 5 and 6 in the PI for SOF
- High response rates (SVR = Cure) are inferred from this limited data set
TREATMENT OF CHRONIC HEPATITIS C: GENOTYPES 5 OR 6

Issues and Controversies
Issues and Controversies

• Cost of Therapy

• When to Defer Therapy
  - Decisions on when to warehouse?

• Degree of Liver Fibrosis
  - How to stage?
How is cost of therapy impacting treatment decisions?
### Patients with GT 5 or 6 HCV: Initial Treatment & Retreatment of Relapsers

<table>
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<th>Regimen and Duration</th>
<th>Regimen Cost</th>
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<td><strong>Recommended Therapy</strong></td>
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<td>Sofosbuvir + Peginterferon + Ribavirin x 12 weeks</td>
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<tr>
<td>Peginterferon + Ribavirin x 48 weeks</td>
<td>$48,000</td>
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### Patients with GT 5 or 6 HCV: Retreatment of Nonresponders

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<td>Sofosbuvir + Peginterferon + Ribavirin x 12 weeks*</td>
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*Note: expert consultation recommended to determine the optimal duration of retreatment of nonresponders in patients with genotypes 5 or 6 and thus treatment duration may extend past 12 weeks and cost may exceed $97,000*
When to defer therapy?
Factors Favoring Treat Now for GT 5 or 6

- 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: GENOTYPES 5 OR 6

Future Treatment Options
Future Regimens for GT 5 or 6

- **Ledipasvir-Sofosbuvir (fixed dose combination)**
  - Ledipasvir: NS5A replication inhibitor
  - Sofosbuvir: NS5b polymerase inhibitor

- **MK-5172 + MK-8742 (fixed dose combination in development)**
  - MK-5172: NS3/4A protease inhibitor
  - MK-8742: NS5A replication inhibitor
Future Regimens for GT 5 or 6

• Ledipasvir-Sofosbuvir (with or without ribavirin)
  - Phase 2 trial with GT 4 or 5 in treatment naïve and experienced
  - Phase 2 trial includes GT 6 in treatment naïve and experienced

• MK-5172 + MK-8742 (fixed dose combination in development)
  - C-EDGE Program
HEPATITIS C: GENOTYPES 5 OR 6

Summary Points
Summary Points for Treatment of Chronic HCV GT 5 or 6

- Infection with GT 5 and 6 accounts for <2% of HCV infections in US
- GT5 highly prevalent in South Africa
- GT6 important in Southeast Asia and especially in the Vietnamese population in the US
- SOF + PEG + RBV recommended for treatment-naïve and relapsers
- Consider SOF + RBV for 24 weeks in interferon ineligible
- Expert consultation recommended for retreatment of nonresponders
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/

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