Treatment of HCV Genotypes 2 and 3

Michael W. Fried, M.D., FAASLD
Professor of Medicine
Director, UNC Liver Center
University of North Carolina
at Chapel Hill
Conflict of Interest Disclosures
Michael W. Fried, M.D.

- **Grants/Research Support Paid to Institution**
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  - AbbVie, BMS, Gilead, TARGET PharmaSolutions

- **TARGET PharmaSolutions stock (Held in Independent Blind Trust)**

- **Speakers Bureau: None**

- **Other Financial Support:** NIH Grants
Patient History

• 54 y/o Caucasian male with genotype 3
• Patient refused as a blood donor in 1993
• 1998: Diagnosed with hepatitis C
• 1999: IFN + RBV: Partial response
• 2003: PEG + RBV: Treatment stopped at 12 weeks
  – Side effects: Irritability, time off from work

• Current status in 2018:
  – Significant progressive fatigue over last few years
Patient History

• Exam
  – Spider angioma + and palmar erythema +
  – No hepatosplenomegaly

• Laboratory data
  – Hemoglobin 15.2 g/dl
  – Platelets = 110,000
  – ALT 86
  – Tbili 1.0
  – Albumin 4.5
  – Fibroscan 14 KPS c/w F4
  – Hepatic U/S: Nodular liver, no masses
Question

With which statement do you most agree?

- Genotype 3 is uncommon and therefore does not warrant further discussion

- Treatment for HCV Geno 3 and cirrhosis is unlikely to be successful with current medications

- This patient would benefit from antiviral therapy
Global Prevalence of Genotype 3

Messina et al, 2015
HCV GT-3 Infection Has Unique Features

- Accelerated fibrosis progression compared to other GT\(^1\)
- Historically lower SVR rates than other genotypes\(^2\)
- Increased HCC incidence compared with non-GT-3\(^3\)
- Increased risk of overall mortality compared with GT-1\(^6\)
- Burden of disease: second most prevalent GT\(^5\)
- Increased prevalence of steatosis compared with GT-1\(^4\)

Adapted from I. Jacobson

Considerations for Selecting Regimens for Genotypes 2 and 3

Treatment naïve vs Treatment-experienced
- PEG IFN
- DAA

Prior NS5A

Non-cirrhotic vs Cirrhotic
- CP A
- CP B

- Compensated cirrhosis:
  - Child’s-Pugh A
  - Goals: Decrease decompensation and HCC, Improve QOL

- Child’s-Pugh B and C
  - Best treated at experienced centers
  - Goals: Obviate need for transplant (?), Improve QOL

Protease inhibitors contraindicated due to alteration in PK

All Regimens may be used

PEG IFN

DAA

CP A

CP B
All-Oral 12-week Combination of Daclatasvir (NS5A) and Sofosbuvir (NUC) in Patients with Genotype 3: ALLY-3

- **ALLY-3**
  - Treatment Naïve
  - 19% w/cirrhosis
  - N=101
  - Daclatasvir + Sofosbuvir
  - SVR
    - 90%

- Prior Treatment
  - 25% w/cirrhosis
  - N=51
  - Daclatasvir + Sofosbuvir
  - SVR
    - 86%

  - SVR F0-F3 = 96% (105/19)
  - SVR F4 = 63% (20/32)

- Key demographics: Cirrhosis= 21%, Prior SOF failures = 7%
- Relapse occurred in 16/152 (11%), most relapsers were cirrhotic

Several other compassionate use studies have demonstrated similar efficacy
Widely used regimen around the world
No longer optimal

Nelson et al, 2015
Hezode et al, 2015
Foster et al, 2015
Sofosbuvir/Velpatasvir in Genotype 3 with/without Compensated Cirrhosis

- Cirrhotic and non-cirrhotic patients randomized to either
  - Sofosbuvir/velpatasvir x 12 weeks
  - Sofosbuvir + RBV x 24 weeks

<table>
<thead>
<tr>
<th>cirrhosis</th>
<th>no cirrhosis</th>
<th>previous treatment</th>
<th>no previous treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>98/160</td>
<td>90/141</td>
<td>91/31</td>
<td>89/33</td>
</tr>
<tr>
<td>93/40</td>
<td>73/44</td>
<td>71/22</td>
<td>58/22</td>
</tr>
<tr>
<td>163/156</td>
<td>156/45</td>
<td>34/31</td>
<td>37/38</td>
</tr>
</tbody>
</table>

Foster et al, 2015
IN GT3 and cirrhosis: RBV mitigates impact of baseline RAS

RAS= Resistant Associated Substitution

Patients with GT3 HCV infection and compensated cirrhosis (N = 204)
Randomized, open label
Treatment naïve and experienced

<table>
<thead>
<tr>
<th>RAS Analysis, n/N (%)</th>
<th>SOF/VEL</th>
<th>SOF/VEL + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of BL RAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79/98 (81)</td>
<td>79/101 (78)</td>
</tr>
<tr>
<td>Yes</td>
<td>19/98 (19)</td>
<td>22/101 (22)</td>
</tr>
<tr>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No BL RAS</td>
<td>76/79 (96)</td>
<td>78/79 (99)</td>
</tr>
<tr>
<td>BL RAS</td>
<td>16/19 (84)</td>
<td>21/22 (96)</td>
</tr>
<tr>
<td>BL Y93H</td>
<td>2/4 (50)</td>
<td>8/9 (89)</td>
</tr>
</tbody>
</table>
Glecaprevir/Pibrentasvir in GT 3: Integrated Analysis of Multiple Studies

**Objective:** Evaluate the efficacy and safety of 8 or 12 weeks of G/P treatment in treatment-naïve patients with chronic HCV GT3 and compensated liver disease (with or without cirrhosis) across 7 phase 2 and 3 clinical trials*

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**GT3**
- No cirrhosis: n = 208
- No cirrhosis: n = 294
- With cirrhosis: n = 69

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* 571 patients across the ENDURANCE-3, EXPEDITION-2, EXPEDITION-4, SURVEYOR-2 (parts 1-3), and MAGELLAN-2 trials

Flamm et al, AASLD, 2017
Glecaprevir/Pibrentasvir in GT 3: Integrated Analysis of Multiple Studies

Flamm et al., AASLD, 2017

<table>
<thead>
<tr>
<th>Tx Weeks</th>
<th>Cirrhosis</th>
<th>OTVF</th>
<th>Relapse</th>
<th>Non-VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>No</td>
<td>1*</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>No</td>
<td>1</td>
<td>4*</td>
<td>9</td>
</tr>
<tr>
<td>12</td>
<td>Yes</td>
<td>1*</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

ITT Analysis

- 8 week: 95/208 (SVR12)
- 12 week: 95/294 (SVR12)
- 12 week: 97/69 (SVR12)

mITT Analysis

- 8 week: 98/203 (SVR12)
- 12 week: 99/284 (SVR12)
- 12 week: 100/67 (SVR12)

Flamm et al, AASLD, 2017
Glecaprevir/Pibrentasvir in GT 3: Integrated Analysis of Multiple Studies

Post-Hoc Analysis of Subgroups
Treatment naïve non-cirrhotic patients

Flamm et al, AASLD, 2017
Elbasvir/Grazoprevir SOF +/- Ribavirin in GT3 Cirrhosis: C-ISLE

Modified Analysis Set (Excludes non-virological failures)

Foster et al., EASL 2017
## Genotype 3
### Treatment Naive

Recommended and alternative regimens listed alphabetically for:

### Treatment-Naive Genotype 3 Patients Without Cirrhosis

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
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</table>
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)
  \(^a\)                                                                         | 8 weeks  | I, A   |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)    | 12 weeks | I, A   |

### ALTERNATIVE

<table>
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<tr>
<th>DURATION</th>
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| Daily daclatasvir (60 mg)
  \(^b\) plus sofosbuvir (400 mg)                                             | 12 weeks | I, A   |

### Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis\(^a\)

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  \(^b\)                                                                         | 12 weeks | I, A   |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)
  \(^c\)                                                                         | 12 weeks | I, A   |

### ALTERNATIVE

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| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)
  /voxilaprevir (100 mg) when Y93H is present                                          | 12 weeks | IIa, B |
| Daily daclatasvir (60 mg)
  \(^d\) plus sofosbuvir (400 mg) with or without weight-based ribavirin\(^c\)     | 24 weeks | IIa, B |
Genotype 3
PEG/RBV Experienced

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

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<th>RECOMMENDED</th>
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<td>12 weeks</td>
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<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(^c)</td>
<td>16 weeks</td>
<td>IIa, B</td>
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<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) when Y93H is present</td>
<td>12 weeks</td>
<td>IIb, B</td>
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Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis\(^a\)

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<th>RECOMMENDED</th>
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<tbody>
<tr>
<td>Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)</td>
<td>12 weeks</td>
<td>IIb, B</td>
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<tbody>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) plus weight-based ribavirin</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(^b)</td>
<td>16 weeks</td>
<td>IIa, B</td>
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POLARIS-1: SOF/VEL/VOX in Prior NS5A Treated Patients

• POLARIS-1
  – Enrolled patients who failed any prior NS5A-containing regimen

Bourliere et al, 2017
GT3 SVR = 94% (51/54) treated with SOF/VEL/VOX
Genotype 3
DAA Experienced

**Recommended regimen for:**
DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis

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<tr>
<td>For patients with prior NS5A inhibitor failure and cirrhosis, weight-based ribavirin is recommended.</td>
<td>12 weeks</td>
<td>IIa, C</td>
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</table>

See HCVguidelines.org
Genotype 2
Global Distribution of HCV Genotypes

Messina et al., 2015
Sofosbuvir/Velpatasvir in Genotype 2 with/without Compensated Cirrhosis

- Cirrhotic and non-cirrhotic patients randomized to either
  - Sofosbuvir/velpatasvir x 12 weeks
  - Sofosbuvir + RBV x 24 weeks

Cirrhosis: ~14%
Prior IFN treatment: ~15%

SVR12

- SOF/VEL 12 weeks: 99, N=134
- SOF/RBV 24 weeks: 94, N=132

ASTRAL-2, ASTRAL-3
Foster et al, 2015
Glecaprevir/Pibrentasvir in Genotype 2 without Cirrhosis

**ENDURANCE-2**
Kowdley et al, 2016

**ITT population:** excludes 6 SOF-experienced patients, all of whom achieved SVR12

**mITT population:** ITT population excluding 1 non-virologic failure who achieved SVR4
Glecaprevir/Pibrentasvir in GT 2 without Cirrhosis: SURVEYOR-II

Included Treatment naïve and treatment experienced (~10%)

mITT excludes patients with non-virological failures
### Genotype 2
#### Treatment Naive

#### Treatment-Naive Genotype 2 Patients Without Cirrhosis

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**ALTERNATIVE**

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#### Treatment-Naive Genotype 2 Patients With Compensated Cirrhosis<sup>a</sup>

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<tr>
<td>Daily daclatasvir (60 mg)&lt;sup&gt;c&lt;/sup&gt; plus sofosbuvir (400 mg)</td>
<td>16 to 24 weeks</td>
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## Genotype 2

**PEG/RBV Experienced**

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### Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis

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<td>16 to 24 weeks</td>
<td>Ila, B</td>
</tr>
</tbody>
</table>
### Genotype 2
**DAA Experienced**

Recommended regimens listed by evidence level for:

**Sofosbuvir + Ribavirin-Experienced, Genotype 2 Patients With or Without Compensated Cirrhosis**

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<td>12 weeks</td>
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Recommended regimen for:

**Sofosbuvir + NS5A-Experienced, Genotype 2 Patients With or Without Compensated Cirrhosis**

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</tbody>
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Treatment of HCV Genotypes 2 and 3

Summary

• Genotype 3 is a common genotype throughout Latin America and increasingly common in U.S. due to opioid epidemic

• Choice of regimens/duration of treatment are affected by
  – Treatment naïve vs prior therapy
  – Prior NS5A inhibitor failure
  – Presence or absence of cirrhosis
    • Compensated vs decompensated

• Near universal effectiveness can be achieved with current regimens

• HCVguidelines .org is a great resource!