HCV Treatment in 2016

Hugo E. Vargas, MD
Professor of Medicine
Mayo College of Medicine
Medical Director, Clinical Trials Office
Vice Chair, Department of Research
Educational Goals

• Caveats:
  • Cannot cover all new therapies
  • Recommendations are still developing
  • Durability and more applicability data outside clinical trials is beginning to emerge
  • Resistance patterns likely to play role in new era
The burden of HCV
Worldwide Burden of Disease due to HCV is Increasing

- WHO estimates 130-170 million people, (3% of world's population) HCV infected and at risk of cirrhosis/HCC
- There are 3 to 4 million new infections/yr
- HCV is responsible for 50–76% of all HCC and 50-60% of all liver transplants in the developed world
- HCV-associated cirrhosis leads to liver failure and death in about 20%-25% of cirrhotic patients
HCV Global Genotype distribution

Messina, Hepatology 2014
Projected Burden of Advanced Fibrosis Over the Next Decade

- 1990 → 77.6% F0/1; cirrhosis = 5%
- 2010 → 41.8% F0/1; cirrhosis = 25%
- 2020 → cirrhosis = 37.2%

Davis, Gastroenterology 2010.
Persons for whom routine HCV testing is recommended

- Persons who ever injected illegal drugs, including those who injected once or a few times many years ago
- Persons who received a blood transfusion or organ transplant before July 1992
- Persons who received clotting factor concentrates before 1987
- Persons who were ever on long-term dialysis
- Children born to HCV-positive women
- Health care, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-positive blood
- Persons with evidence of chronic liver disease
- Persons born between 1945-1965
US population with chronic HCV infection
3.2 million

HCV detected
1.6 million (50%)

Referred to care
1.0 – 1.2 million (32%-38%)

HCV RNA test
630,000 – 750,000 (20-23%)

Liver biopsy
380,000 – 560,000 (12%-18%)

Treated
220,000 – 360,000 (7-11%)

Successfully treated
170,000 – 200,000 (5-6%)

Holmberg, NEJM 2013.
How do we approach treatment?
Direct-Acting Antivirals for Hepatitis C

NS3/4 Protease Inhibitors
- Simeprevir
- Asunaprevir
- Paritaprevir/r
- Vedroprevir
- Grazoprevir

NS5B Polymerase Inhibitors
- Sofosbuvir
- Radalbuvir (GS-9669)
- Beclabuvir
- Dasabuvir

NS5A Inhibitors
- Ledipasvir
- Ombitasvir
- Daclatasvir
- Elbasvir
- Velpatasvir

Protease Inhibitors:
- Simeprevir
- Asunaprevir
- Paritaprevir/r
- Vedroprevir
- Grazoprevir

Polymerase Inhibitors:
- Sofosbuvir
- Radalbuvir (GS-9669)
- Beclabuvir
- Dasabuvir

Translation and polyprotein processing
Receptor binding and endocytosis
Transport and release
Virion assembly
Fusion and uncoating
RNA replication
RNA
ER Jumen
The new paradigm: SVR=Cure

• Why?:
  • HCV does not persist
    • No known intracellular reservoirs
    • No DNA intermediaries

• In theory if we can impact viral replication with therapy, we can achieve clearance once infected hepatocytes clear
The new paradigm: SVR=Cue

• HOWEVER
  • Resistance can create problems.

Why?
  • HCV replicates very rapidly (>10^{12} virions/day)
  • RNA polymerase has low fidelity (1 error/10K base)
  • The reading frame has no overlaps

• Based on modeling, patients can harbor variants which render them resistant **before** exposure to DAA’s
Glossary for this new era:

- **Resistant variant**: A phenotypically different strain that has higher EC$_{50}$ than wild type

- **Viral fitness**: Complex interplay of mutational changes that render strain able to effectively replicate
  - May require resistance and other mutations that even/beat advantages present in wild type

- **Barrier to resistance**: Threshold in the antiviral to be overcome by viral mutants to reach resistance
  - (e.g. number of base changes to effect AA changes that render strain resistant)
Viral populations

Intermediate viral populations, detected by population sequencing (if >5% of the quasispecies) or by cloning and sequencing

Major viral populations, detected by population sequencing

Minor viral populations, detected by next-generation sequencing techniques

Chevaliez, Gastroenterology 2012
Treatment Recommendations

- The current recommended regimens (will focus in USA predominantly)
Treatment Recommendations

• The goal of treatment of HCV-infected persons is to **reduce all-cause mortality and liver-related health adverse consequences**.
  • Includes:
    • ESLD
    • HCC

• Treatment is recommended for all patients with chronic HCV infection, **except those with short life expectancies** that cannot be remediated by treating HCV, by transplantation, or by other directed therapy.

Patients with short life expectancies owing to liver disease should be managed in consultation with an **expert**.

AASLD/IDSA Guidance Panel
Treatment Recommendations

• Basics:
  • Viral genotype
  • Titers
  • Fibrosis
    • FibroScan
    • MR elastography
    • Serological tests
  • RAV analysis:
    • Strongly consider in pts who have been expose to DAA’s and in pts with G1a and perhaps 3 (tests are not widely available yet for the latter)

AASLD/IDSA Guidance panel
Treatment Recommendations

• Consider vaccination: HBV, HAV
• Review HIV risk factors and test
• Discuss non-infected sexual partner testing and precautions
• Ensure that they understand SVR does not preclude re-infection
• Discuss how you will design treatment and follow up
  • Do not forget cirrhosis complications and f/u
Treatment Recommendations

• These regimens change rapidly
  • Please check recommendations frequently

• Be mindful of DDI, many and very important
  • Liver Transplant
  • HIV/HCV co-infected

• Rather than restrict on stage of disease look for signs of poor compliance
Treatment Recommendations

- Inexperienced treaters should:
  - Evaluate treatment NAÏVE patients
  - Make sure that they have been staged (rely on TE)
  - Understand all the DDIs that could complicate management
  - Recognize the source for information in this rapidly changing area
DDI screening
www.hep-druginteractions.org

INTERACTION CHARTS FOR PHONES AND TABLETS

HEP iChart – NEW VERSION AVAILABLE

A new version of the interaction app for mobile devices is now available. The new app includes tablet support for Android devices and is fully compatible with the latest versions of iOS.

Please delete the existing app from your device and download the new version from the App Store or Google Play (search for HEP iChart).

WEBCASTS - HIV2014, Glasgow
Meeting Report - 65th AASLD (The Liver Meeting)
Meeting Report - HIV2014, Glasgow
Drug Interactions – Boceprevir or telaprevir and eltabropog
Click here for previous news items
SITE UPDATES

Elbasvir/Grazoprevir
Zepatier® (elbasvir/grazoprevir) has been approved by the FDA and is now available on the wa...

Comedications – some new, some moved
The latest update to the comedications list

> more
Recommendations for Testing, Managing, and Treating Hepatitis C

http://www.hcvguidelines.org/
## DRUG CLASS SUMMARY

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3/4A Protease inhibitor</td>
<td>Simeprevir</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir +RTV</td>
</tr>
<tr>
<td></td>
<td>Asunaprevir</td>
</tr>
<tr>
<td></td>
<td>Grazoprevir</td>
</tr>
<tr>
<td>NS5A Inhibitor</td>
<td>Daclatasvir</td>
</tr>
<tr>
<td></td>
<td>Ledipasvir</td>
</tr>
<tr>
<td></td>
<td>Elbasvir</td>
</tr>
<tr>
<td></td>
<td>Ombitasvir</td>
</tr>
<tr>
<td></td>
<td>Velpatasvir</td>
</tr>
<tr>
<td>NS5B non-nucleoside polymerase inhibitor</td>
<td>Dasabuvir</td>
</tr>
<tr>
<td></td>
<td>Beclabuvir</td>
</tr>
<tr>
<td>NS5B nuc polymerase inhibitor</td>
<td>Sofosbuvir</td>
</tr>
</tbody>
</table>
## DRUG CLASS SUMMARY
### Long Term

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3/4A Protease inhibitor</td>
<td>ABT 493</td>
</tr>
<tr>
<td></td>
<td>Voxilaprevir (GS 9857)</td>
</tr>
<tr>
<td></td>
<td>Vedroprevir (GS-9451)</td>
</tr>
<tr>
<td>NS5A Inhibitor</td>
<td>ABT 530</td>
</tr>
<tr>
<td></td>
<td>MK 8408</td>
</tr>
<tr>
<td>NS5B non-nucleoside polymerase inhibitor</td>
<td>Radalbuvir (formerly GS-9669)</td>
</tr>
<tr>
<td>NS5B nucleoside polymerase inhibitor</td>
<td>MK-3682 (formerly IDX21437)</td>
</tr>
</tbody>
</table>
Highly Efficacious Treatments Are Not Enough!

All HCV patients

Diagnosis AND treatment

CURE

PEG-IFN/RBV

100%

20%

10%

95% SVR

100%

20%

19%

95% SVR + HIGH Dx/TX

100%

90%

85%
Treatment Recommendations

The current recommended regimens focus on **optimal** regimens.
Genotype 1

**SOF/VEL 12wks**
- a- Decomp cirrhosis, add RBV*
- b- Decomp cirrhosis, and SOF or NS5A failure, add RBV 24wks

**EBV/GZV 12wks**
- a- In G1a check RAVs to NS5A, if + 16wks
- b- NS3/PI+PEG-IFN/RBV TE, add RBV, and if +RAVs to NS5A 16wks
- c- Not for post-LT or Decomp cirrhosis
Genotype 1

SOF/SMV 12wks

• \textit{a-If NS5A TE, avoid in G1a if +NS3 Q80K}

SOF/DCV 12wks

• \textit{a-Cirrhosis, or NS3/PI+PEG-IFN/RBV TE, +/- RBV 24wks}
• \textit{b-Decomp cirrhosis, add RBV*}
Genotype 1

**SOF/LDV 12wks**
- a-Naïve, non-cirrhotic, non-African American, and <10^6 copies 8wks
- b-Decomp cirrhosis, or NS3A/PI+PEG-IFN/RBV TE with cirrhosis, or post-LT, add RBV*
- c-SOF/RBV TE, add RBV 12wks, if cirrhosis, add RBV 24wks

**OBV/PTV/R/DVR 12wks**
- a-G1a or 1 add RBV
- b-Cirrhosis, caution (per FDA), 1b 12wks, G1a or 1, add RBV 24wks
Genotype 2

**SOF/VEL** 12 wks
  *a*-Decomp cirrhosis, add RBV

**SOF/DCV** 12wks
  *a*-Cirrhosis, 16-24wks
  *b*-Decomp cirrhosis, add RBV 12wks
  *c*-SOF/RBV TE, +/- RBV 24wks
Genotype 3

SOF/VEL 12wks
   a-Decomp cirrhosis, or PEG-IFN/RBV or SOF/RBV TE, add RBV

SOF/DCV 12wks
   a-Cirrhosis, +/- RBV 24wks
   b-SOF/RBV TE, add RBV 24wks
   c-Decomp cirrhosis, add RBV 12wks
Genotype 4

**SOF/VEL 12wks**

- Decomp cirrhosis, add RBV*
- SOF or NS5A TE, add RBV 24wks

**SOF/LDV 12wks**

- Decomp cirrhosis, add RBV*
- PEG-IFN/RBV TE and cirrhosis, add RBV*
- SOF TE, add RBV
Genotype 4

**EBV/GZV 12wks**

a - TE, if failure to suppress virus on prior tx, add RBV

b - Not for post-LT or Decomp cirrhosis

**OBV/PTV/R +RBV 12wks**

a - Cirrhosis, caution (per FDA), add RBV

b - PEG-IFN/RBV TE, add RBV
Genotype 5

**SOF/VEL 12wks**

**SOF/LDV 12wks**

\textit{a-SOF TE or post-LT, add RBV}
Genotype 6

SOF/VEL 12wks

SOF/LDV 12wks
    a-SOF TE or post-LT add RBV
http://www.hcvguidelines.org/

Recommendations for Testing, Managing, and Treating Hepatitis C
What’s new in late 2016-2017

• SOF/VEL approved in the USA and Europe
• New PI/NS5A combination in late trials
• New SOF/VEL/Voxilaprevir
Pooled ASTRAL Studies (ASTRAL-1, ASTRAL-2, ASTRAL-3)

SOF/VEL Single Tablet Regimen for 12 Wks

<table>
<thead>
<tr>
<th>GT</th>
<th>SVR12 (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99</td>
<td>323/328</td>
</tr>
<tr>
<td>2</td>
<td>99</td>
<td>237/238</td>
</tr>
<tr>
<td>3</td>
<td>95</td>
<td>264/277</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>116/116</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>34/35</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>41/41</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>1015/1035</strong></td>
</tr>
</tbody>
</table>

SOF/VEL + Voxilaprevir for 12w in TE GT1-6

• Open-label phase II studies

Previously treated* GT1-6 HCV (N = 128) → SOF/VEL 400/100 mg QD + GS-9857 100 mg QD

Wk 12

Compensated cirrhosis: 48%

• Previous treatment experience
  • NS5A inhibitor: 27%
  • Non-NS5A inhibitor DAAs: 52%
  • No previous DAA: 21%

Results: SVR12 Overall and by Genotype

- Overall: 99% (127/128)
- GT 1: 100% (63/63)
- GT 2: 100% (21/21)
- GT 3: 97% (34/35)
- GT 4, 6: 100% (9/9)

♦ One patient relapsed at post-treatment week 8

Results: SVR12 by Subgroup

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Prior NS5A Experience</th>
<th>No. of DAA Classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>0*</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>≥2</td>
<td></td>
<td>≥2</td>
</tr>
</tbody>
</table>

SVR12 (%)

67/67 60/61 92/93 35/35 27/27 35/36 65/65

*GT 2-6 patients who failed prior Peg-IFN+RBV regimens.
Results: Resistance Analysis

- **Deep sequencing with 1% assay cutoff.**

  - 100% SVR12 (51/51)
  - 60% Baseline RAVs (77/128)
  - 40% No Baseline RAVs (51/128)
  - 20% NS5A RAVs only
  - 15% NS3 RAVs only
  - 23% Multiple class RAVs
  - 2% NS5B RAVs only

- 99% SVR12 (76/77)

*Deep sequencing with 1% assay cutoff.*
SOF/VEL + RBV for 24w After SOF/VEL Failure

- Single-arm trial
  
  No SVR in previous phase II trials of SOF/VEL (n = 41) or SOF/VEL + GS-9857 (n = 28) (N = 69)

- Cirrhosis: 26%; previous relapse: 99%
- HCV genotype: GT1a: 46% GT1b: 7% GT2: 20% GT3: 26%

Gane EJ, et al. EASL 2016. Abstract PS024
SOF/VEL + RBV Retreatment

- Overall SVR12: 91%
  - GT1 (n = 34): 97%
  - GT2 (n = 14): 91%
  - GT3 (n = 17): 76%
- No effect of RAVs on SVR12 for GT1 or GT2
- 9/11 (82%) pts with GT3 HCV and Y93H achieved SVR12

Gane EJ, et al. EASL 2016. Abstract PS024
SURVEYOR-II Part 2: ABT-493 + ABT-530 ± RBV in GT3 and Cirrhosis

- Open-label, partially randomized phase II study\(^1\)
- ABT-493 + ABT-530: pangenotypic second-generation DAA combination\(^2,3\)
  - Minimal renal excretion (< 1%)

SURVEYOR-II Part 2\(^1\):
Naive GT3 HCV infection and compensated cirrhosis (N = 48)

\(Wk\ 12\)

1. ABT-493 300 mg QD + ABT-530 120 mg QD (n = 24)
2. ABT-493 300 mg QD + ABT-530 120 mg QD + RBV 800 mg QD (n = 24)

ABT-493 + ABT-530 ± RBV in GT3 HCV and Cirrhosis

- 18/48 pts had NS3 and/or NS5A RAVs at BL
- No discontinuations due to AEs
- No ALT elevations; 1 pt with grade 3 total bilirubin elevation

Kwo PY, et al. EASL 2016. Abstract LBO1
MAGELLAN-I: ABT-493 + ABT-530 \pm RBV for 12w in DAA-TE GT1

• Open-label, randomized phase II trial

DAA-TE GT1 HCV infection without cirrhosis (N = 50)

Previous treatment experience
• NS5A inhibitor but not PI: 16%
• PI but not NS5A inhibitor: 50%
• PI and NS5A inhibitor: 34%
• NS5B inhibitor: 54%

82% of pts with NS3 and/or NS5A RAVs at BL (1% threshold)

MAGELLAN-I
ABT-493 + ABT-530 ± RBV for 12w in DAA-TE GT1

- No treatment-related SAEs or discontinuations
- No ALT elevations, grade 3/4 laboratory abnormalities
- Presence of RAVs did not appear to affect SVR12 rates:
  - No RAVs: 100%
  - NS3 only: 100%
  - NS5A only: 90%
  - NS3 and NS5A: 94%

HCV after Liver Transplantation

• The change here has been even more impressive

• HCV continues to be significant etiology for LT in USA

• Untreated, universal recurrence

• DAA era has created very solid options for treatment
HCV in Liver transplantation

• Goal is to minimize post LT damage to the graft

• Debate about pre-LT treatment vs post-LT treatment

• Each approach has advantages that need consideration

• May be impacted by prevalence locally
HCV in Liver transplantation

Pre-Liver Transplantation:

- Eradicate disease
  - Avoid LT
  - Prevent post-LT graft damage
  - Prevent on-list mortality

- Limitations
  - PI may be deleterious in decompensated cirrhosis
  - SOF is restricted by renal dysfunction
  - SVR is approx 10% lower than in comp cirrhosis
LDV/SOF + RBV for Treatment of HCV in Patients with Decompensated Cirrhosis or Post-Transplant Recurrence

Cohort A: Advanced Liver Disease

- Group 1: CTP B; 7-9, n = 25
- Group 2: CTP C; 10-12, n = 25

Cohort B: Post-Transplant

- Group 3: F0-F3, no decomp., n = 50
- Group 4: CTP A; 5-6, n = 50
- Group 5: CTP B; 7-9, n = 25
- Group 6: CTP C; 10-12, n = 25
- Group 7: FCH, Wk 0, Wk 12, Wk 24, n = 25

Study Weeks

- Wk 0
- Wk 12
- Wk 24

All arms continue with 5 years of long-term follow-up for clinical outcomes
Prospective, multicenter study of 12 or 24 weeks of LDV/SOF + RBV in TN and TE HCV GT 1 and 4 patients with CTP B (N=59) or CTP C (N=49) clinically decompensated cirrhosis

108 patients randomized 1:1 to 12 or 24 weeks of treatment

Stratified by CTP class B [7-9] or C [score 10–12]*

RBV dosing: dose escalation, 600–1200 mg/d

Charlton et al Gastro 2015
Results: SVR12

SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Error bars represent 90% confidence intervals.

Charlton et al Gastro 2015.
Change From Baseline to Follow-Up Week 4

CPT B
12 wk (n=30)*
24 wk (n=29)*

CPT C
12 wk (n=23)*
24 wk (n=26)*

*Missing FU-4: n=2 CPT B 12 wk; n=4 CPT B 24 wk; n=2 CPT C 12 wk; n=7 CPT C 24 wk.

Charlton et al Gastro 2015.
Overall Safety Summary

- Related SAEs: Anemia (2), hepatic encephalopathy, peritoneal hemorrhage
- Early discontinuations: Sepsis, hepatic encephalopathy, peritoneal hemorrhage
- Deaths: septic shock (2), multi-organ failure and septic shock (2), oliguric renal failure, cardiac arrest

### SOLAR-1: LDV/SOF + RBV in Decompensated Cirrhosis

**Patients, n (%)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CTP B 12 Weeks n=30</th>
<th>CTP B 24 Weeks n=29</th>
<th>CTP C 12 Weeks n=23</th>
<th>CTP C 24 Weeks n=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>29 (97)</td>
<td>27 (93)</td>
<td>23 (100)</td>
<td>26 (100)</td>
</tr>
<tr>
<td>Grade 3/4 AE</td>
<td>2 (7)</td>
<td>8 (28)</td>
<td>6 (26)</td>
<td>11 (42)</td>
</tr>
<tr>
<td>SAEs</td>
<td>3 (10)</td>
<td>10 (34)</td>
<td>6 (26)</td>
<td>11 (42)</td>
</tr>
<tr>
<td>Tx Related SAEs</td>
<td>2 (7)</td>
<td>0</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>D/C due to AE</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td>2 (9)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Charlton et al Gastro 2015.
SOF/VEL ± RBV in HCV Patients with Decompensated Cirrhosis (Astral 4)

SOF/VEL 12 wk | SOF/VEL+RBV 12 wk | SOF/VEL 24 wk
---|---|---
Overall: 83/94 | 88/96 | 50
GT 1: 75/82/77/60 | 65/68/65/71 | 11/13/7/6
GT 2: 65/71 | 7/14 | 50
GT 3: 85/50 | 86/65/68
GT 2, 4, and 6: 100/100

Curry et al NEJM 2016
ALLY-1: Multicenter, Open-Label Phase 3 Study

- **Primary endpoint:** SVR12 in GT1 in each cohort
- **12 weeks of treatment:** DCV 60 mg + SOF 400 mg + RBV
  - RBV initially 600 mg/day, adjusted to 1000 mg/day based on Hgb levels and CrCl
- **Advanced cirrhosis patients with treatment interrupted by liver transplantation could receive an additional 12 weeks of treatment immediately post-transplant**

### Study Groups

**Advanced cirrhosis**
- N = 60
- DCV 60 mg QD + SOF 400 mg QD + RBV

**Post-liver transplant**
- N = 53
- DCV 60 mg QD + SOF 400 mg QD + RBV

Follow-up:
- Week 0:
  - DCV 60 mg QD + SOF 400 mg QD + RBV
- Week 12:
  - SVR12
- Week 24:
  - SVR12
- Week 36:
Demographic and Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Advanced cirrhosis</th>
<th>Post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 60</td>
<td>N = 53</td>
</tr>
<tr>
<td>Age, median (range) years</td>
<td>58 (19–75)</td>
<td>59 (22–82)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>38 (63)</td>
<td>38 (72)</td>
</tr>
<tr>
<td>Treatment-naive, n (%)</td>
<td>24 (40)</td>
<td>22 (42)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>57 (95)</td>
<td>51 (96)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>25 (42)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Non-Hispanic/Latino</td>
<td>35 (58)</td>
<td>40 (75)</td>
</tr>
<tr>
<td>HCV RNA, mean (SD), log_{10} IU/mL</td>
<td>6.01 (0.62)</td>
<td>6.61 (0.71)</td>
</tr>
<tr>
<td>HCV genotype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>34 (57)</td>
<td>31 (58)</td>
</tr>
<tr>
<td>1b</td>
<td>11 (18)</td>
<td>10 (19)</td>
</tr>
<tr>
<td>2</td>
<td>5 (8)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>6 (10)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>4</td>
<td>4 (7)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>IL28B non-CC genotype, n (%)</td>
<td>47 (78)</td>
<td>40 (75)</td>
</tr>
<tr>
<td>Estimated METAVIR score, n (%)a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0–F2</td>
<td>-</td>
<td>23 (43)</td>
</tr>
<tr>
<td>F3</td>
<td>-</td>
<td>13 (25)</td>
</tr>
<tr>
<td>F4</td>
<td>-</td>
<td>16 (30)</td>
</tr>
<tr>
<td>Not reported</td>
<td>-</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

a Estimated METAVIR scores were derived from Fibrotest scores: F0–F2, 0–0.58; F3, >0.58–0.74; F4, >0.74–1.00.
Baseline Disease Characteristics by CPT Stage
Advanced cirrhosis cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Class A N = 12</th>
<th>Class B N = 32</th>
<th>Class C N = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites present, n (%)</td>
<td>0</td>
<td>21 (66)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Encephalopathy present, n (%)</td>
<td>2 (17)</td>
<td>19 (59)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Native MELD score, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>7 (58)</td>
<td>7 (22)</td>
<td>0</td>
</tr>
<tr>
<td>10–15</td>
<td>5 (42)</td>
<td>20 (63)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>16–20</td>
<td>0</td>
<td>5 (16)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>21–25</td>
<td>0</td>
<td>0</td>
<td>3 (19)</td>
</tr>
<tr>
<td>&gt; 25</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Albumin, median (range) g/dL</td>
<td>3.7 (3.0–4.3)</td>
<td>3.2 (2.6–4.4)</td>
<td>2.5 (2.0–3.4)</td>
</tr>
<tr>
<td>INR, median (range)</td>
<td>1.2 (1.1–1.4)</td>
<td>1.4 (1.0–1.9)</td>
<td>1.7 (1.2–3.9)</td>
</tr>
<tr>
<td>T bilirubin, median (range) mg/dL</td>
<td>0.9 (0.4–1.7)</td>
<td>1.6 (0.6–4.4)</td>
<td>3.0 (1.1–6.4)</td>
</tr>
<tr>
<td>Platelets, median (range) × 10⁹ cells/L</td>
<td>94 (41–179)</td>
<td>86 (35–182)</td>
<td>72 (35–147)</td>
</tr>
<tr>
<td>α-fetoprotein, median (range) ng/mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13.0 (3.4–49.6)</td>
<td>13.3 (1.8–86.2)</td>
<td>7.7 (1.8–149)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Entry criteria: MELD scores 8–40.

<sup>b</sup> Included 6 HCC patients: 1 CP A, 2 CP B, 3 CP C
No difference by gender, age, *IL28B*, or HCV RNA in the advanced cirrhosis cohort with GT 1
SVR12 by Child-Pugh Class
Advanced cirrhosis cohort, all genotypes

SVR12, %

Child-Pugh class
A: 92
B: 94
C: 56

Ascites
- No: 21 (37)/23
- Yes: 29 (37)/28

HE
- No: 22 (37)/23
- Yes: 28 (37)/10

Albumin, g/dL
- >3.5: 10 (18)/41 (49)
- 3.5 to 2.8: 30 (31)/8 (12)
- <2.8: 18 (10)/3 (3)

INR
- >1.7: 23 (37)/33 (37)
- 1.7 to 2.3: 31 (10)/6 (12)
- <2.0: 18 (18)/9 (9)

T bili, mg/dL
- >2.0: 11 (11)/8 (8)
- 2.0 to 3.0: 3 (3)/3 (3)
- <2.0: 18 (18)/9 (9)
MELD Scores – Baseline to Posttreatment Week 12
Advanced cirrhosis cohort

Change in MELD score: □ Decrease  ■ Increase  □□ No change

* Patient did not achieve SVR12.
HCV in Liver transplantation

Post-Liver Transplantation:
- Safer drug profile
- Allows the use of F0 hepatic grafts from HCV+ donors
- No penalty for waiting in terms of SVR

- DDI may be a limitation for choice of DAA
  - PI’s have CNI dosing implications
223 patients randomized 1:1 to 12 or 24 weeks of treatment
- ≥3 months from liver transplant
- No hepatocellular carcinoma
- Stratified at screening: F0–F3, CTP A, B, C
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>F0-F3 n=111</th>
<th>CTP A n=51</th>
<th>CTP B n=52</th>
<th>CTP C n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>59 (26-72)</td>
<td>60 (21-81)</td>
<td>61 (37-72)</td>
<td>60 (57-66)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>91 (82)</td>
<td>41 (80)</td>
<td>45 (87)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>99 (89)</td>
<td>41 (80)</td>
<td>45 (87)</td>
<td>8 (89)</td>
</tr>
<tr>
<td>Median HCV RNA, log_{10} IU/mL (range)</td>
<td>6.6 (2.4-7.8)</td>
<td>6.6 (4.6-7.6)</td>
<td>6.4 (4.4-7.2)</td>
<td>6.3 (5.8-6.8)</td>
</tr>
<tr>
<td>GT 1a, n (%)</td>
<td>80 (72)</td>
<td>34 (67)</td>
<td>38 (73)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>IL28B non-CC, n (%)</td>
<td>90 (81)</td>
<td>43 (84)</td>
<td>44 (85)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Median years from OLTx (range)</td>
<td>2.9 (0.4-18.2)</td>
<td>8.1 (0.8-23.3)</td>
<td>5.6 (0.9-22.5)</td>
<td>5.2 (1.2-15.5)</td>
</tr>
<tr>
<td>Prior HCV treatment, n (%)</td>
<td>87 (78)</td>
<td>46 (90)</td>
<td>44 (85)</td>
<td>8 (89)</td>
</tr>
<tr>
<td>MELD (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>N/A</td>
<td>28 (55)</td>
<td>13 (25)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>10-15</td>
<td>N/A</td>
<td>20 (39)</td>
<td>33 (63)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>16-20</td>
<td>N/A</td>
<td>3 (6)</td>
<td>4 (8)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>21-25</td>
<td>N/A</td>
<td>0</td>
<td>2 (4)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Ascites, n (%)</td>
<td>2 (2)</td>
<td>2 (4)</td>
<td>40 (77)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Encephalopathy, n (%)</td>
<td>1 (1)</td>
<td>3 (6)</td>
<td>23 (44)</td>
<td>7 (78)</td>
</tr>
</tbody>
</table>

Charlton et al Gastro 2015.
SOLAR-1: LDV/SOF + RBV

Results: SVR12

<table>
<thead>
<tr>
<th></th>
<th>LDV/SOF + RBV 12 Weeks</th>
<th>LDV/SOF + RBV 24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0–F3</td>
<td>96/96</td>
<td>98/96</td>
</tr>
<tr>
<td>CTP A</td>
<td>96/96</td>
<td>96/96</td>
</tr>
<tr>
<td>CTP B</td>
<td>85/83</td>
<td>83/83</td>
</tr>
<tr>
<td>CTP C</td>
<td>60/67</td>
<td>67/67</td>
</tr>
</tbody>
</table>

SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Error bars represent 2-sided 90% exact confidence intervals.

Charlton et al Gastro 2015.
Change in MELD Score

Change from Baseline to Follow-Up Week 4

CTP A Patients (n=48)

12 Wk (n=23)

24 Wk (n=25)

CTP B Patients (n=41)

12 Wk (n=21)

24 Wk (n=20)

Missing FU: n=3 CTP A 12 wk; n=5 CTP B 12 wk; n=5 CTP B 24 wk

Charlton et al Gastro 2015.
## Overall Safety Summary

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>F0-F3</th>
<th>CTP A</th>
<th>CTP B</th>
<th>CTP C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AEs</strong></td>
<td>55 (100)</td>
<td>55 (98)</td>
<td>25 (96)</td>
<td>24 (96)</td>
</tr>
<tr>
<td><strong>Grade 3‒4 AEs</strong></td>
<td>15 (27)</td>
<td>14 (25)</td>
<td>4 (15)</td>
<td>7 (28)</td>
</tr>
<tr>
<td><strong>Serious AEs</strong></td>
<td>6 (11)</td>
<td>12 (21)</td>
<td>3 (12)</td>
<td>4 (16)</td>
</tr>
<tr>
<td><strong>Serious and related AEs</strong></td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>2 (8)</td>
<td>2 (8)</td>
</tr>
<tr>
<td><strong>Treatment DC due to AE</strong></td>
<td>0</td>
<td>2 (4)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Treatment emergent death</strong></td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

- AEs leading to DC: shortness of breath, hemoperitoneum, thoracic aorta aneurysm dissection, seizure, elevated ALT/AST, dyspnea
- Treatment-emergent death: progressive multifocal leukoencephalitis, thoracic aorta aneurysm dissection, internal bleeding, complications of cirrhosis

[Charlton et al Gastro 2015](#)
LDV/SOF + RBV for Post-LT Recurrence

- In HCV post LT, treatment with LDV/SOF+RBV for 12 or 24 weeks resulted in:
  - High rates of SVR12, irrespective of disease severity or duration of therapy (ie, 12 = 24 weeks)
  - Early post-treatment improvements in bilirubin and albumin
  - Decreases in MELD scores
  - No on-treatment virologic failure
  - LDV/SOF+RBV for 12 or 24 weeks in post LT pts was safe and well tolerated with low rates of treatment discontinuation due to AEs

Charlton et al Gastro 2015,
SVR12 by HCV Genotype

Advanced cirrhosis cohort
N = 60

Post-transplant cohort
N = 53

SVR12, %

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Advanced Cirrhosis</th>
<th>Post-Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>76</td>
<td>97</td>
</tr>
<tr>
<td>1b</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
No difference by gender, age, *IL28B*, or HCV RNA in the advanced cirrhosis cohort with GT 1
SVR12 by Child-Pugh Class
Advanced cirrhosis cohort, all genotypes

Child-Pugh class

<table>
<thead>
<tr>
<th>Class</th>
<th>SVR12, %</th>
<th>No Ascites</th>
<th>Yes Ascites</th>
<th>No HE</th>
<th>Yes HE</th>
<th>&lt;1.7 INR</th>
<th>1.7 to &gt;2.3 INR</th>
<th>&lt;2.8 Albumin, g/dL</th>
<th>2.8 to &gt;3.5 Albumin, g/dL</th>
<th>&gt;3.5 Albumin, g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>92</td>
<td>21/23</td>
<td>29/37</td>
<td>22</td>
<td>28/37</td>
<td>10/11</td>
<td>41/49</td>
<td>6/8</td>
<td>3/3</td>
<td>33/37</td>
</tr>
<tr>
<td>B</td>
<td>94</td>
<td>22/23</td>
<td>28/37</td>
<td>28</td>
<td>30/31</td>
<td>22/18</td>
<td>67/75</td>
<td>10/9</td>
<td>3/3</td>
<td>33/37</td>
</tr>
<tr>
<td>C</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>56/75</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SVR12, %
Take home points

• In post LT setting:
  • Treat early (before advanced fibrosis develops)
  • Mind IS DDI (if using PI regimens)
  • Mind renal dysfunction (SOF based regimens)
  • Expect very solid results
Take home points

• In pre LT setting:
  • Cirrhosis can and will decompensate when treating
  • List decompensated cirrhotic pts
  • There may be advantage to wait
    • HCV+ grafts
  • Expect lower results
Questions

• Can 3D regimen be used?
• Can SOF/VEL be used in this setting?
• Can patients be delisted?