Treatment Challenges in Transplant Patients

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Director of Hepatology
University of Colorado Denver
<table>
<thead>
<tr>
<th>Disclosures</th>
<th>Roche/Genentech, Vertex, GlobeImmune, BMS, Abbvie, Eisai, HGS/Novartis, Pfizer, Gilead, Janssen/Tibotec, Abbvie/Abbott</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advisory Boards:</td>
<td>Roche-Genentech, HGS/Novartis, BMS, Three Rivers/Kadmon, Vertex, Abbvie, BioTest, Boehringer-Ingelheim</td>
</tr>
<tr>
<td>Consulting:</td>
<td>Merck, Centocor, Galectin</td>
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<tr>
<td>DSMB:</td>
<td>Source, HepQuant LLC</td>
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<td>Stock/Ownership:</td>
<td>HepQuant LLC</td>
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<td>Management:</td>
<td>Roche/Genentech, Schering/Merck, Vertex, GlobeImmune, Gilead, HGS/Novartis, BMS, Pfizer, Source, Eisai, GSK, Pharmassett, Ortho Biotech, Janssen/Tibotec, Abbvie</td>
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</tbody>
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Key Questions

1. Should we treat HCV pre- or post-transplant?

2. What are the current antiviral choices?

3. What are the potential future choices?
1. SVR: Avoid LTx

2. SVR: Prevent Recurrence of HCV

3. On Rx at LTx: Suppress HCV to Prevent Recurrence (pTVR)
### Possible Options

<table>
<thead>
<tr>
<th>Pan-GT:</th>
<th>PEG/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF/PEG/RBV</td>
</tr>
<tr>
<td></td>
<td>SOF/RBV**</td>
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<tr>
<td></td>
<td>3D+r ± RBV</td>
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</table>

** Only FDA-recommended Pre-transplant treatment option. Otherwise, treatment of clinically decompensated cirrhosis is considered “off-label”.
PEG/RBV + BOC or TPV
(no data with SIM or SOF)
**Impact of Disease Severity**

**CUPIC French open-access Study**

<table>
<thead>
<tr>
<th>Albumin</th>
<th>Platelet Count $\mu$L$^{-1}$</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 100,000</td>
<td>≤ 100,000</td>
<td></td>
</tr>
<tr>
<td>≥ 3.5 g/dL</td>
<td>N</td>
<td>306</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>% SVR</td>
<td><strong>55%</strong></td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td>% SAE/Death</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
<td>&lt; 3.5 g/dL</td>
<td>N</td>
<td>31</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>% SVR</td>
<td>29%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>% SAE/Death</td>
<td>16%</td>
<td><strong>51%</strong></td>
</tr>
</tbody>
</table>

CUPIC Caveat

Albumin: < 3.5 g/dL
Platelet Count: < 100,000 µL

These laboratory features indicate high-risk for treatment-related SAEs with PEG/RBV plus BOC or TPV.
PEG/RBV/TPV: pTVR

% HCV RNA negative

Acceptable Options

Pan-GT: 
- PEG/RBV
- SOF/PEG/RBV
- SOF/RBV
- LDV/SOF ± RBV#

GT 1 only: 
- TT (SMV, TPV, or BOC)
- SMV/SOF ± RBV
- 3D+r ± RBV

# Daclatasvir (DAC) may substitute for ledipasvir (LDV) for GT 2 and 3.
SOF/RBV in Cirrhosis with Portal Hypertension
(N=50, 1:1 Rx:No Rx Cntrl for 24 Wks, 48 Wks Rx, HVPG 16 (7-29), CTP<10)

% with undetectable HCV RNA

Rx extended to 48 weeks. SVR in most. HVPG improved in a subset. EASL 2015.
Achieving pTVR


% Achieving pTVR

<table>
<thead>
<tr>
<th>Group</th>
<th>Multi</th>
<th>Single</th>
<th>Multi</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG/RBV</td>
<td>25</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>SAE</td>
<td>46%</td>
<td>31%</td>
<td>18%*</td>
</tr>
<tr>
<td>Death</td>
<td>15%</td>
<td>3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>%HCC</th>
<th>62%</th>
<th>39%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD</td>
<td>12</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

* No SAE was attributed to SOF. Rate of SAEs was similar to rate of SAEs in Controls in LADR-A2ALL.
SOF/RBV: pTVR is related to Duration of undetectable HCV RNA

% Achieving pTVR

1. SMV: FDA-approved 2013
2. SOF: FDA-approved 2013
3. SMV/SOF: FDA-approved 12/2014

AASLD/IDSA Guidelines: “Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for IFN-ineligible patients with HCV genotype 1 infection, regardless of subtype.” “........is recommended for retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility.” The basis for these recommendations were an average SVR of 72% in 211 Rx-Naïve GT1 patients treated with 24 Wks SOF/RBV. SIM/SOF, 12 Wks, might be a more effective regimen in these patients.
**SMV/SOF**

**COSMOS Cohort 2: F3/F4, 54% Null Responders**

% SVR12

![Bar Chart](chart.png)

- **12 Weeks**
  - RBV: 93/24/27
  - No RBV: 93/13/14

- **24 Weeks**
  - RBV: 93/27/30
  - No RBV: 100/16/16

*AASLD Guidelines January 30, 2014; Presented at EASL 2013, 2014 and AASLD 2013.*
HCV TARGET
1012 Treated with SMV/SOF ± RBV (303 evaluable for SVR4)

% SVR4

Presented at AASLD 2014. RBV did not improve SVR overall or in any subpopulation.
Lower SVR4: Low albumin, GT1a, Prior Decomp, TT failure. AEs: Anemia - RBV. SAEs 5 to 6%.
12 Deaths – 9 in patients with cirrhosis.
1. SOF: FDA-approved 2013

2. LDV/SOF: FDA-approved 12/2014

FDA approved without RBV. Addition of RBV may allow shortening 24 week course to 12 weeks.
LDV/SOF in >500 Patients with GT1 Cirrhosis

% SVR 12

- **Rx-Naïve**
  - 12 Wk: 96%
  - 12 Wk + RBV: 98%
  - 24 Wk: 97%
  - 24 Wk + RBV: 100%

- **Rx-Experienced**
  - 12 Wk: 90%
  - 12 Wk + RBV: 96%
  - 24 Wk: 98%
  - 24 Wk + RBV: 100%

Results: SVR12
GT 1 and 4, CTP Class B and C

6 subjects (2 CPT B/24 Wk, 1 CPT C/12 Wk and 3 CPT C/24 Wk) excluded (transplant on study); 3 subjects CPT C/24 Wk have not reached SVR12. Error bars represent 90% confidence intervals.
Laboratory Results: Change in MELD Score From Baseline Through Follow-up Week 4

<table>
<thead>
<tr>
<th>CPT B</th>
<th>CPT C</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 wk (n=30)*</td>
<td>12 wk (n=23)*</td>
</tr>
</tbody>
</table>

*Missing FU-4: n=2 CPT B 12 wks; n=4 CPT B 24 wks; n=2 CPT C 12 wk; n=7 CPT C 24 wk.
3D/r + RBV
(Paritaprevir/r + Ombitasvir + Dasabuvir + RBV)

1. 3D/r ± RBV: FDA-approved 12/2014
High SVR12 Rates with 3D + RBV in GT1a Treatment-Naïve and -Experienced Patients With Cirrhosis

$p$ values from Fisher’s exact test
Improvement from baseline in conjugated bilirubin at PTW12

<table>
<thead>
<tr>
<th></th>
<th>12-week arm</th>
<th>24-week arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL mean</td>
<td>0.30</td>
<td>0.31</td>
</tr>
<tr>
<td>PTW12 mean</td>
<td>0.19</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean Δ from BL at PTW12 (95% CI)</td>
<td>-0.10 (-0.12, -0.09)</td>
<td>-0.13 (-0.15, -0.11)</td>
</tr>
</tbody>
</table>
Improvement from baseline in albumin levels at PTW12

![Box plot showing improvement in albumin levels from baseline to PTW12 for 3D + RBV treatment.]

<table>
<thead>
<tr>
<th></th>
<th>12-week arm</th>
<th>24-week arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL mean (g/dL)</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>PTW12 mean (g/dL)</td>
<td>4.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Mean Δ from BL at PTW12 (95% CI)</td>
<td>0.2 (0.17, 0.24)</td>
<td>0.3 (0.21, 0.31)</td>
</tr>
</tbody>
</table>

Normalization of liver–related laboratory parameters in HCV GT1-infected patients with cirrhosis | ACG 2014 | 20 October 2014
Others
Multi-DAA in HCV GT1 Cirrhosis

% SVR 12

LDV/SOF (Gilead) 3D r (Abbvie) 3D (BMS) 2D (Merck)

493/513 241/263 187/201 115/123

RBV ± + ± ±
Duration 12 vs 24 12 vs 24 12 12 vs 18
Genotype 1a/1b 1a 1a/1b 1a/1b
Phase 3 3 3 2
Genotypes 2 and 3
Genotype 2

<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>Expected SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis, Rx-Naive 12 Wks</td>
<td>95%¹</td>
</tr>
<tr>
<td>Cirrhosis, Rx-Naive 12 Wks</td>
<td>94%¹</td>
</tr>
<tr>
<td>No Cirrhosis, Rx-Experienced 12 or 16 Wks</td>
<td>97%²</td>
</tr>
<tr>
<td>Cirrhosis, Rx-Experienced 12 Wks</td>
<td>60%²,*</td>
</tr>
<tr>
<td>Cirrhosis, Rx-Experienced 16 Wks</td>
<td>78%²</td>
</tr>
</tbody>
</table>

¹ Data from FISSION and POSITRON and ² FUSION.
*In VALENCE, an SVR of 78% (7/9) was achieved with 12 weeks SOF/RBV. Given the discordancy in results, optimal duration of SOF/RBV for Rx-experienced cirrhosis is unknown.
Genotype 3 (based on VALENCE* study)

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<th>Treatment Duration</th>
<th>Expected SVR</th>
</tr>
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<tbody>
<tr>
<td>No Cirrhosis, Rx-Naive</td>
<td>24 Wks (87/92)</td>
</tr>
<tr>
<td>Cirrhosis, Rx-Naive</td>
<td>24 Wks (12/13)</td>
</tr>
<tr>
<td>No Cirrhosis, Rx-Exp</td>
<td>24 Wks (85/98)</td>
</tr>
<tr>
<td>Cirrhosis, Rx-Exp</td>
<td>24 Wks (29/47)</td>
</tr>
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An alternative for IFN-eligible patients could be SOF/PEG/RBV for 12 weeks. In PROTON and ELECTRON studies (Rx-Naïve) 38/39 patients (97%) achieved SVR. In LONESTAR-2 (Rx-Experienced), 83% (10/12) achieved SVR.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Treatment Options</th>
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<tbody>
<tr>
<td>Pan-GT</td>
<td>SOF/RBV</td>
</tr>
<tr>
<td></td>
<td>LDV/SOF ± RBV #</td>
</tr>
<tr>
<td>GT 1 only</td>
<td>SMV/SOF ± RBV</td>
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<td>3D+r ± RBV</td>
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# Daclatasvir (DAC) may substitute for ledipasvir (LDV) for GT 2 and 3.
Post-Transplant
Treatment Goals

1. SVR

2. Improve Graft and Patient Survival
## Possible Options

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<td>SMV/SOF ± RBV</td>
</tr>
<tr>
<td></td>
<td>3D+r ± RBV</td>
</tr>
</tbody>
</table>

** None of these post-transplant treatment options are FDA-approved. Treatment of post-transplant patients is considered “off-label”.”
PEG/RBV: SVR

Gane EJ, Agarwal K. Am J Transplant 2014;14:994-1002.
PEG/RBV + BOC or TPV
(no data with SIM or SOF)
CRUSH C and French Multicenter Studies

Adverse Events
- 20% Early discontinuation
- 25-59% Hospitalizations
- 56% Blood transfusions
- 14-40% Renal insufficiency
- 3-17% Rejection
- 7-8% Liver-related death

## Acceptable Options

<table>
<thead>
<tr>
<th>Pan-GT</th>
<th>PEG/RBV</th>
<th>SOF/PEG/RBV</th>
<th>SOF/RBV</th>
<th>LDV/SOF ± RBV#</th>
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<td>TT (SMV, TPV, or BOC)</td>
<td>SMV/SOF ± RBV</td>
<td>3D+r ± RBV</td>
<td></td>
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* Daclatasvir (DAC) may substitute for ledipasvir (LDV) for GT 2 and 3.
SOF/RBV ± PEG
SOF/RBV
All GTs, Rx-N or –Exp, CTP ≤ 7, MELD ≤ 17, No Decomp, 63% F3/F4, N=40

% with undetectable HCV RNA

Week 4 | EOT | SVR 4 | SVR 12 | SVR 24
---|---|---|---|---
100 | 100 | 77 | 70 | 70

HCV TARGET

143 Treated with SMV/SOF ± RBV (68 evaluable for SVR4)

% SVR4

<table>
<thead>
<tr>
<th></th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>94</td>
</tr>
<tr>
<td>29/31</td>
<td></td>
</tr>
<tr>
<td>156/180</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>86</td>
</tr>
<tr>
<td>32/37</td>
<td></td>
</tr>
</tbody>
</table>

Presented at AASLD 2014. Anemia from RBV was a common AE. 8.5% had an SAE.
3D/r + RBV
(Paritaprevir/r + Ombitasvir + Dasabuvir + RBV)
ABT450/r/Ombitasvir/Dasabuvir/RBV
GT1, Rx-N, <F3, No Decomp, N=34

% with undetectable HCV RNA

<table>
<thead>
<tr>
<th></th>
<th>Week 4</th>
<th>EOT</th>
<th>SVR 4</th>
<th>SVR 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100</td>
<td>97</td>
<td>96</td>
<td></td>
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</table>

Results: SVR12
GT 1 or 4: Post-Transplant F0–F3, CPT A, B, C

Error bars represent 2-sided 90% exact confidence intervals.
8 CPT B 24 Week and 1 CPT C 24 Week subjects have not reached the Week 12 post treatment visit.
Laboratory Results: Change in MELD Score From Baseline Through Follow-up Week 4

CPT A Patients (n=48)

12 Wk (n=23) 24 Wk (n=25)

CPT B Patients (n=41)

12 Wk (n=21) 24 Wk (n=20)
Post-transplant Options

Pan-GT: SOF/RBV
LDV/SOF ± RBV#

GT 1 only: SMV/SOF ± RBV
3D+r ± RBV

Longer duration of 24 weeks and addition of RBV may be required, particularly for liver recipients with cirrhosis.

# Daclatasvir (DAC) may substitute for ledipasvir (LDV) for GT 2 and 3.
Paradigm Shift

1. From IFN-based Treatment
   • Low efficacy (both pre- and post-LT)
   • High Toxicity (especially in cirrhosis)
   • Limited Applicability

2. To IFN-free Treatments
   • Improved efficacy (both pre- and post-LT)
   • Limited Toxicity (both pre- and post-LT)
   • Treat either pre- or post-LT
“Anybody can jump a motorcycle. The trouble begins when you try to land it.”  Evel Kneivel
Drug-Drug Interactions

Clinical Pharmacist
Resources for DDIs

• Outstanding – University of Liverpool (David Back, Editorial Board, EASL reps); sponsored by Janssen, MSD, Roche, Vertex:
  – http://www.hep-druginteractions.org

• FDA:

• Other Online Resources –
  – Epocrates
  – Micromedex, Lexicomp and Others
Can Hepatitis C Virus be Cured?

Yes

But, someone has to pay for it!

Panic: $5 \times 10^6$ cases @ $10^5$ $/$case

= $500,000,000,000$
The Price of NOT Treating Chronic Hepatitis C

- Study of economic burden of chronic hepatitis C in the US, stratified by disease severity, based upon a large health insurance claims database.

- Based on data from 53,796 patients with chronic hepatitis C – 78% without cirrhosis, 7% with compensated cirrhosis, 15% with ESLD

- Overall Annual Healthcare Costs per Patient: $24,176

- Annual Costs per Patient Without Cirrhosis: $17,277

- Annual Costs per Patient With Compensated Cirrhosis: $22,752

- Annual Costs per Patient With ESLD: $59,995

- Estimated US Average Charges per LTx in 2011: $577,100

http://digestive.niddk.nih.gov/ddiseases/pubs/livertransplant/
http://digestive.niddk.nih.gov/before-the-transplant/financing-a-transplant/the-costs/
1. MELD “Purgatory”?  
   • MELD decreases with SVR  
   • Portal hypertension and clinical complications persist

2. HCV+ Donor?  
   • HCV+ recipient – wait to treat?  
   • HCV- recipient – accept liver?  
   • Renal transplantation – wait to treat?  
   • Renal candidate HCV+ or - - accept kidney?