Hepatitis C Treatment in Patients with Advanced Fibrosis

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Royalties: Up-to-date

Overview

DAA Therapy in Patients with Advanced Fibrosis/Cirrhosis

- Identifying and assessing severity of cirrhosis
  - Liver transplantation: when is it appropriate to consider?
- HCV treatment – unique aspects of decompensated patients
- HCV treatment and HCC
- Post-DAA treatment monitoring in patients with cirrhosis
Establishing if Cirrhosis is Present

- Palmar erythema, spider angioma
- Symptoms of ascites, variceal bleeding, hepatic encephalopathy
- Plt < 150,000/µl + AST > ALT
  - FIB-4 ≥3.25 or APRI ≥2
  - FibroTest or Fibrosure
- US: nodular liver, splenomegaly, varices, enlarged PV
  - TE → LSM > 12.5 kPa

Routine lab tests

Liver Imaging
- Ultrasound
- Liver Stiffness Measurement

If non-invasive tests are discrepant and still unclear if cirrhosis

Liver biopsy

Stages of Cirrhosis and Relationship to Portal Hypertension

Compensated
- No PHTN
- Mild PHTN (HVPG > 5 < 10 mmHg)
- Clinically Significant Portal Hypertension (CSPH)
  - HVPG ≥ 10 mmHg

No varices
Varices

Decompensated
- Variceal bleed
- No ascites/HE
- HVPG ≥ 12 mmHg

Further decompensated
- Recurrent variceal bleed
- ± HE and ascites
- HVPG ≥ 20 mmHg

HVPG: hepatic venous pressure gradient
Normal 0-5 mm Hg

Shung DL and Garcia-Tsao G, Hepatology 2017;65(3):1038
Stage Needs to be Established Prior to Treatment

• Non-invasive tests to stage liver fibrosis have not been validated in patients after SVR
  – Diagnostic accuracy of non-invasive tests after SVR is suboptimal → underestimates fibrosis

• Cirrhosis warrants specific surveillance tests
  – EGD to assess for varices
  – US/CT scan ± AFP to assess for liver cancer every 6 months → should be done pre-treatment


How to Assess Severity of Cirrhosis?

- **Child-Pugh-Turcotte Class**
  - Albumin, bilirubin, INR, ascites, HE
- **MELD-Na score**
  - Creatinine, bilirubin, INR, Sodium

- Both measures predict short-term mortality
- Reflect hepatic reserve (liver synthetic dysfunction and severity of portal HT)
**Calculate Child-Pugh Class**

<table>
<thead>
<tr>
<th>Child-Turcotte-Pugh Classification for Severity of Cirrhosis</th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>

*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

- **Class A** = 5 to 6 points (least severe liver disease)  <5%
- **Class B** = 7 to 9 points (moderately severe liver disease)  25%
- **Class C** = 10 to 15 points (most severe liver disease)  50%

1-year post-operative mortality

**MELD-Na Score and 90-day Mortality**

Na=135, T Bili 3.0, INR 1.4, Cr 1.6, MELD-NA=20

An Important Question to Ask

- Should liver transplantation be considered?
  - MELD ≥12-15
  - Any symptoms of decompensation (ascites, HE, varices)
  - Liver cancer (if small and confined to liver)

- If potentially eligible – hold on treatment
  - For many transplant candidates, best option is treating after transplant
  - Deferring HCV treatment allows earlier access to transplant (eligible for HCV+ donors)
  - Detailed discussion of risks and benefits essential

DAA Treatment in Patients with Cirrhosis

Importance of Child-Pugh Score
Which Patient with Cirrhosis has the Most DAA Treatment Options?

- Genotype 1A
- Grade 2-3 varices on EGD
- No ascites or HE
- Na 138, Creatinine 1.2,
- INR 1.5, platelet count 70K
- AST 56, ALT 48, total bilirubin 1.5, albumin 3.6

- Genotype 1A
- Grade 1 varices on EGD
- No HE or ascites
- Na 135, Creatinine 0.8
- INR 1.5, platelet count 70K
- AST 56, ALT 48, total bilirubin 2.0, albumin 2.7

CPT score =6

CPT score =8

Defining Decompensated Cirrhosis for Treatment Purposes

**COMPENSATED**

- Childs A

  AND

  Have NOT experienced any of the following: jaundice, ascites, hepatic encephalopathy or history of variceal hemorrhage

**DECOMPENSATED**

- Childs B or C

  OR

  Have experienced one or more of the following: jaundice, ascites, variceal hemorrhage, hepatic encephalopathy
DAA Options for Patients with Cirrhosis

Child-Pugh score = 8

- Daclatasvir + Sofosbuvir
- Simeprevir + Sofosbuvir
- Ledipasvir-Sofosbuvir
- Paritaprevir/r-Ombitasvir +Dasabuvir
- Sofosbuvir-Velpatasvir
- Velpatasvir
- Grazoprevir
- Glecaprevir-pibrentasvir
- Velpatasvir-Voxilprevir

+ Ribavirin

SOF-VEL ± RBV for G1-6 Patients with Child-Pugh B Cirrhosis: The Role of RBV

- ASTRAL-4
- HCV GT 1-6 patients with CPT B cirrhosis

RBV should be included in treatment of all patients with decompensated cirrhosis, especially G3

SVR12 Rates Among Patients with Cirrhosis by Child-Pugh Score

LDV-SOF + RBV for 12 wks

<table>
<thead>
<tr>
<th></th>
<th>CP-A</th>
<th>CP-B</th>
<th>CP-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall:</td>
<td>96/108</td>
<td>89/102</td>
<td>81/96</td>
</tr>
<tr>
<td>GT1:</td>
<td>439/513</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT4:</td>
<td></td>
<td>96/102/5/6</td>
<td>75/91/3/5</td>
</tr>
</tbody>
</table>


Why Higher Rates of Virologic Failure with Advanced Cirrhosis?

- Decreased hepatocyte mass
- Decreased drug uptake
- Decreased drug delivery
- Distorted sinusoidal architecture leads to increased resistance
- Portosystemic collaterals
- Splenomegaly
Summary

Unique Aspects of Treating Patients with Decompensated Cirrhosis (CP-B/C)

- Fewer DAA options
  - Protease inhibitor are contraindicated
  - Ribavirin needed to enhance efficacy
- Tolerability and safety need closer scrutiny
  - Ribavirin-associated side effects
  - Risks of worsening decompensation
- Lower rates of SVR
  - Very limited treatment options for those with DAA failure

HCV DAA Therapy and Liver Cancer
Risk of De Novo HCC After DAA Therapy

Patients differ in DAA era:
- Older
- More advanced cirrhosis (longer duration of cirrhosis)
- Coexistent risks for NAFLD

Meta-Analysis of De Novo HCC after IFN and DAA Therapy

5,521 treated in 19 studies from Europe, Asia, SA, NA
6,002 treated in 7 studies from Europe. 1 Asian

a) IFN: HCC occurrence

b) DAA: HCC occurrence

1.14/100 person-yrs

2.96/100 person-yrs

Waziry R, J Hepatol 2017, in press
Effect of Age and Duration of Follow-up on Occurrence of HCC

DAA treated patients have average follow-up which is shorter than IFN-treated patients.

DAA treated patients are on average 8 years older than IFN-treated patients.

Waziry R, J Hepatol 2017, in press

Risk of De Novo HCC After DAA Therapy

### MULTIVARIATE Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>aRR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN</td>
<td>1.00</td>
<td>--</td>
</tr>
<tr>
<td>DAA</td>
<td>0.68</td>
<td>0.56</td>
</tr>
<tr>
<td>Avg follow-up</td>
<td>0.75</td>
<td>0.04</td>
</tr>
<tr>
<td>Average age</td>
<td>1.06</td>
<td>0.12</td>
</tr>
</tbody>
</table>

In meta-regression, adjusting for differences in age and length of follow-up, type of treatment was no longer associated with HCC.

DAA and IFN risks NOT different.

In HCV-associated liver cirrhosis:

- Natural history ~3–7% per year
- SVR (interferon-based therapy) <1.5% per year
- Adjusted SVR (DAA-based tx) <1.5% per year

HCC occurrence
SVR Rates Reduced in Patients with HCV and “Active” HCC

Predictors of DAA Treatment Failure

<table>
<thead>
<tr>
<th>Covariates</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate regimen</td>
<td>2.85</td>
<td>1.32-6.16</td>
<td>0.008</td>
</tr>
<tr>
<td>Active tumor</td>
<td>8.49</td>
<td>3.90-18.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.99</td>
<td>0.99-1.0</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, race, CPT class, genotype and anti-HBc

Why Higher Rates of Virologic Failure in Patients with HCC?

Prenner S et al, J Hepatology, 2017, in press
HCC and DAA Therapy

- Treatment with DAAs does not appear to increase the risk of de novo HCC
  - Higher rates reported in DAA era reflect older patient population with more advanced cirrhosis
- SVR rates are lower in patients with HCC
  - If possible, wait until after HCC is treated then treat HCV
- Curative therapy available for small HCCs → importance of surveillance to detect early

Management of Patients with Advanced Fibrosis After the Cure
DAA Therapy Reduces But Does Not Eliminate Risk of Liver Complications

Decompensated cirrhosis treated with DAA therapy
N=406 treated
N=261 untreated

Risk of HCC in Patients Treated with DAA Therapy

Main risk is presence of cirrhosis

1.82 vs 0.34/100 person-years (cirrhosis vs no cirrhosis)

~70% reduction in rates of HCC if SVR achieved

39% had cirrhosis

Kanwal F, Gastroenterology 2017
Predictors of HCC in Patients Achieving SVR

Those most consistently reported across studies:

<table>
<thead>
<tr>
<th>Categories</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Older age</td>
</tr>
<tr>
<td>[Viral]</td>
<td>Genotype 3</td>
</tr>
<tr>
<td>Disease-related</td>
<td>Cirrhosis*</td>
</tr>
<tr>
<td></td>
<td>Lower platelet count</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>Alcohol use</td>
</tr>
</tbody>
</table>

*Variably defined: APRI≥2, FIB-4 ≥3.25, elastography, biopsy


Monitoring Required Post-SVR in Patients with Advanced Fibrosis

<table>
<thead>
<tr>
<th>At Risk For</th>
<th>Monitor With</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variceal bleeding</td>
<td>EGD screening</td>
<td>Yearly if decompensated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Every 2-3 years if compensated</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Ultrasound + AFP</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>New onset decompensation</td>
<td>MELD and clinical evaluation</td>
<td>Every 6 months if compensated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Every 1-3 months if decompensated</td>
</tr>
</tbody>
</table>
Suggested Triage of Patients with Cirrhosis

**CP-A**
No history of ascites, HE, variceal bleeding
- Experienced HCV treater (non-GI/Liver specialist)
- Caveat: Willingness to conduct for pre and post-SVR monitoring

**CP-B or CP-C**
Any history of decompensation
- Liver/GI specialist
- Linkage with liver transplant center helpful

Liver cancer

Reasons to Triage Patients with CP-B/C Cirrhosis to Specialists

- Liver complications can occur before, during and after treatment
- Liver transplantation needs to be considered
  - Timing of HCV treatment influenced by whether patient is on list or not
- Fewer drug options, greater risk of toxicity
- Long-term follow-up for liver complications needs even after SVR
  - Especially risk of HCC
Treatment of HCV in Patients with Advanced Fibrosis

- Establish if cirrhosis present pre-treatment; determine severity using Child-Pugh score and MELD
- Treatment of decompensated patients quite different from compensated
- Risk of HCC is not increased by treatment with DAA but risk for HCC persists after cure
- Long-term follow-up for liver-related complications is essential

Thank-you!