What are the remaining questions in Hepatitis C management?

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Prince of Songkla University, Thailand
What is the Optimal management for CHC decompensated cirrhosis?
Key Considerations for CHC
Decompensated Cirrhosis

- Treatment options are more limited than for patients without cirrhosis or with compensated cirrhosis
  - SVR rates are generally lower
- Protease inhibitors are not recommended for CTP B or C
- Continuing role for ribavirin
  - Initial low dose
- Extend duration to 24 wks if RBV ineligible
SOF/VEL/VOX and G/P and not recommended in patients with decompensated cirrhosis

<table>
<thead>
<tr>
<th>DAA</th>
<th>Exposure Level (relative to patients with normal hepatic function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voxilaprevir</td>
<td>5-fold</td>
</tr>
<tr>
<td>Pibrentasvir</td>
<td>11-fold</td>
</tr>
</tbody>
</table>
ALLY-1 SOF/DCV+RBV: SVR12 by Child-Pugh Class

Advanced cirrhosis cohort, all genotypes

Bar chart showing SVR12% by Child-Pugh class and other liver function tests.

- Child-Pugh class
- Ascites
- HE
- Albumin, g/dL
- INR
- T bili, mg/dL

HE = hepatic encephalopathy
The SOLAR-1 STUDY: LDV/SOF+RBV Treatment in HCV genotype 1 or 4 with decompensated cirrhosis

RBV: initial dose of 600mg daily

### SVR 12 (%)

<table>
<thead>
<tr>
<th>CTP class</th>
<th>12 W</th>
<th>24 W</th>
<th>12 W</th>
<th>24 W</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP class B</td>
<td>56</td>
<td>52</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>CTP class C</td>
<td>43</td>
<td>48</td>
<td>86</td>
<td>87</td>
</tr>
</tbody>
</table>

### Serious Adverse event

<table>
<thead>
<tr>
<th>CTP</th>
<th>12W</th>
<th>24 treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class B</td>
<td>10%</td>
<td>34%</td>
</tr>
<tr>
<td>Class C</td>
<td>26%</td>
<td>42%</td>
</tr>
</tbody>
</table>

ASTRAL-4: SOF/VEL ± RBV in HCV Patients with Decompensated Liver Disease

The Hong Kong Association for the Study of Liver Diseases

The Hong Kong Association for the Study of Liver Diseases

The Hong Kong Association for the Study of Liver Diseases

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SOF/VEL + RBV resulted in highest SVR12 in patients with decompensated liver disease

*Patient with nondetectable drug levels at time of virologic failure.

Charlton M, et al., AASLD, 2015, #LB-13
### Treatment of HCV genotype 1 or 4,6 with decompensated cirrhosis CTP class B or C

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Ribavirin</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir (60mg) / Sofosbuvir (400mg)</td>
<td>With low initial dose of RBV</td>
<td>12-24 week</td>
</tr>
<tr>
<td>Sofosbuvir (400mg) / Velpatasvir (100mg)</td>
<td>With low initial dose of RBV</td>
<td>12 week</td>
</tr>
<tr>
<td>Daclatasvir (60mg) + Sofosbuvir (400mg)</td>
<td>With low initial dose of RBV</td>
<td>12 week</td>
</tr>
</tbody>
</table>
## Treatment of HCV genotype 2, 3 decompensated cirrhosis

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Ribavirin</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir (400mg) / Velpatasvir (100mg)</td>
<td>Low initial dose of RBV</td>
<td>12 week</td>
</tr>
<tr>
<td>Daclatasvir (60mg) + Sofosbuvir (400mg)</td>
<td>Low initial dose of RBV</td>
<td>12 week</td>
</tr>
</tbody>
</table>
Treatment of CHC decompensated cirrhosis: considering risk and benefit

- Improving MELD score and improve survival
- Delisting from Liver transplantation

Risk
- Non-use HCV positive donor
- Delay liver transplantation
- MELD purgatory

Benefit
Long term clinical benefits of DAAs treatment in decompensated cirrhosis

- 454 cirrhotic patients with either CP (B) or decompensated cirrhosis
- Treated with DAAs 12 weeks or 24 weeks: 386 SVR+ 66 no SVR and 5 LFU

Transplant free survival

Novo HCC development

Successful HCV treatment was associated with significantly fewer deaths and liver cancer development

Cheung MCM, Royaume-Uni, EASL 2018, Abs. LBP-009 actualisé
Long term clinical benefits of DAAs treatment in decompensated cirrhosis

Patients outcome according to pre-treatment baseline MELD score

- Died
- Transplanted or on waitlist
- Alive without transplant need

 ulaMELD < 16 (n = 391)
MELD 16-20 (n = 42)
MELD > 20 (n = 14)

2/3 of patients alive with a baseline MELD score < 16 avoid liver transplantation.

Cheung MCM et al. EASL 2018, Abs. LBP-009
Delisting due to clinical improvement with DAA Therapy in HCV decompensated cirrhosis waiting list for liver transplantation.
CHC decompensated cirrhosis listed for Liver transplantation

HCV patient LT listed for de-compensated cirrhosis

Risk of pre LT death:
Higher for MELD >18

Risk that DAAs may work at disadvantage
Higher for MELD >18

Possibility of de-listing:
Higher for MELD <18

Belli LS. et al. ELITA. J Hepatol 2017; 67; 585-602.
Management of liver transplant candidate CH-C: according to MELD

CH-C decompensated cirrhosis waiting list for LT

- MELD <16: DAA Therapy
- MELD 16-20: DAA Therapy
- MELD 21-25: Individual consideration Risk vs Benefit
- MELD > 25: Post-LT DAA therapy

- Improved MELD score > 3 points
- Improved Albumin > 0.5 g/dL

- Waiting list in inactive position
- Waiting list in active position

Belli LS. et al. ELITA. J Hepatol 2017; 67.
A lack of improvement to CPT A status
MELD score <15
BE3A Score: Predicting probability of achieving CTP class A

No Encephalopathy

BMI < 25

No Ascites

ALT >60 IU/L

Albumin >3.5 g/dL

# BE3A Score

<table>
<thead>
<tr>
<th>Category</th>
<th>Findings</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>&lt;25 kg/m²</td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>ALT</td>
<td>&gt;1.5 × ULN</td>
<td>1</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5 g/dL</td>
<td>1</td>
</tr>
</tbody>
</table>

ULN, upper limit of normal

---

Kaplan Meier curves of achieving CPT A and death/transplant with BE3A score

A

![Graph showing Kaplan Meier curves for CPT A achievement and death/transplant over time with BE3A score.

<table>
<thead>
<tr>
<th>BE3A 0</th>
<th>BE3A 1</th>
<th>BE3A 2</th>
<th>BE3A 3</th>
<th>BE3A 4-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
<td>219</td>
<td>180</td>
<td>95</td>
<td>22</td>
</tr>
<tr>
<td>99</td>
<td>206</td>
<td>161</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>89</td>
<td>181</td>
<td>131</td>
<td>49</td>
<td>7</td>
</tr>
<tr>
<td>19</td>
<td>25</td>
<td>17</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

B

![Graph showing Kaplan Meier curves for death/transplant over time with BE3A score.

<table>
<thead>
<tr>
<th>BE3A 0</th>
<th>BE3A 1</th>
<th>BE3A 2</th>
<th>BE3A 3</th>
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<td>180</td>
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<td>22</td>
</tr>
<tr>
<td>97</td>
<td>208</td>
<td>175</td>
<td>91</td>
<td>22</td>
</tr>
<tr>
<td>83</td>
<td>187</td>
<td>160</td>
<td>77</td>
<td>21</td>
</tr>
<tr>
<td>14</td>
<td>29</td>
<td>26</td>
<td>15</td>
<td>4</td>
</tr>
</tbody>
</table>

BE3A score in predicting a chance of achieving CPT A at 36 weeks after initiation of DAA therapy in CH-C decompensated cirrhosis.

What is the Optimal time to treat CHC in patients with HCC?
A retrospective cohort study: CHC cirrhotic patients with or without HCC who failed DAA therapy

Relapsed at 12 weeks post treatment: 48% in those with active HCC when starting DAA compared with 0% in those with no active HCC, p =0.04

Patients with inactive HCC or DAA started after tumor removal achieved high SVR similar to those without HCC

The cumulative incidence of HCC among CHC patients who achieved SVR, stratified by cirrhosis status

Cirrhotics

Without Cirrhotics

<table>
<thead>
<tr>
<th>Cirrhosis status</th>
<th>at risk</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
<th>Year 7</th>
<th>Year 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis neg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>18</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cirrhosis pos</td>
<td>1548</td>
<td>1145</td>
<td>875</td>
<td>643</td>
<td>433</td>
<td>247</td>
<td>95</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

When is the Optimal time to treat acute hepatitis C
**Acute HCV infection: issues need to be considered**

<table>
<thead>
<tr>
<th><strong>acute HCV infection = infection &lt; 6 month</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40% may clear the infection spontaneously</td>
</tr>
<tr>
<td>High Response to Interferon-alpha</td>
</tr>
<tr>
<td>Most patients are asymptomatic</td>
</tr>
<tr>
<td>Infection remains unidentified</td>
</tr>
<tr>
<td>DAA therapy is very effective in chronic HCV</td>
</tr>
<tr>
<td>Lack of cost-effectiveness study</td>
</tr>
</tbody>
</table>

Acute HCV infection – All-oral DAA therapy?
The HepNet Acute-HCV-IV Study

Deterding et al., Lancet Infect Dis. 2017 Feb;17(2):215-222
Acute HCV infection – All-oral DAA therapy?
The HepNet Acute-HCV-IV Study

Deterding et al., Lancet Infect Dis. 2017 Feb;17(2):215-222
Management of acute HCV infection

Acute HCV infection

Delayed treatment

Unacceptable

Monitoring for 12-16 weeks

Persistent HCV infection

SOF/VEL for 6 weeks

Acceptable

Persistent infection > 6 months

Chronic hepatitis C

Treatment as CH-C

Spontaneous clearance of HCV infection

Advise
Are there any patients unable to treat effectively?
Estimated clearance time for RAVs selected upon treatment failure

RAVs (%)

- NS5A Inhibitors
- Non-nucleoside NS5B polymerase inhibitors
- Protease inhibitors
- Sofosbuvir

10%

days months years

# Sofosbuvir/velpatasvir/voxilaprevir duration of therapy

## Treatment-experienced patients without cirrhosis or with compensated cirrhosis (Child-Pugh A)

<table>
<thead>
<tr>
<th>Prior regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV genotype</td>
<td></td>
</tr>
<tr>
<td>1,2,3,4,5, or 6</td>
<td>NS5A inhibitors</td>
</tr>
<tr>
<td>1a or 3</td>
<td>Sofosbuvir without NS5A inhibitor</td>
</tr>
</tbody>
</table>

Pearlman BL. Aliment Pharmacol Ther. 2018;48:914-923
<table>
<thead>
<tr>
<th>Prior regimen</th>
<th>Duration</th>
<th>Compensated cirrhosis (Child-Pugh A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve</td>
<td>No cirrhosis</td>
<td>8 weeks</td>
</tr>
<tr>
<td>HCV genotype</td>
<td>1,2,3,4,5, or 6</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NS5A inhibitor w/o NS3/A inhibitor</td>
<td>16 weeks</td>
</tr>
<tr>
<td>1</td>
<td>NS3/4A inhibitor w/o NS5A inhibitor</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1,2,3,4,5, or 6</td>
<td>Interferon, peginterferon, ribavirin ± sofosbuvir but w/o NS3/4A or NS5A inhibitor</td>
<td>8 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Interferon, peginterferon, ribavirin ± sofosbuvir but w/o NS3/4A or NS5A inhibitor</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

Pearlman BL. Aliment Pharmacol Ther. 2018;48:914-923
CHC decompensated cirrhosis with RASs

NS5A inhibitor

NS 3/4A Protease inhibitor

Protease Inhibitors, Voxilaprevir or Glecaprevir, are not recommended in patients with decompensated cirrhosis.
In order to Achieve HCV Elimination in 2030

How to manage with treatment barriers

How to prevent HCV re-infection
Conclusion

- Treatment of CHC decompensated cirrhosis needs to consider and balance between risk and benefit
- Consider the optimal strategy for CHC treatment whether before or after liver transplantation according to MELD or BE3A score
- Due to the report of high relapsed rate after DAA therapy in patients with HCC, starting DAA therapy after achieving inactive HCC is reasonable
- Treatment strategy for acute hepatitis C should be considered according to the availability and national policy as well as patient agreement
- Effective and safe rescue therapy for CHC decompensated with RAVs, particularly NS5A inhibitors, is still unmet need
Thank you