Hepatitis C: Making Sense of it All

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Difficult to Keep It All Straight!

AASLD/ISDA Guidelines
http://hcvguidelines.org

- Continuously updated
- Sets the standard of care for HCV in the US
- May be useful in obtaining insurance approval
Currently Available DAA Drug Classes

**Protease inhibitors**
- NS3/4 inhibitors

**NS5a inhibitors**

**Polymerase inhibitors**
- NS5b inhibitors
  - Nucleoside
  - Non-nucleoside

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**Protease Inhibitors (NS3/4)**

*What you need to know*

**Low barrier to resistance**
- Resistance shared among same generation drugs
- New generations have a higher barrier to resistance

**Metabolized in the liver**
- Increased drug-drug interactions
- Avoid in decompensated liver disease

**Examples**
- Telaprevir, boceprevir, simeprevir, paritaprevir
  - *Coming soon*: grazoprevir (2nd generation)
NS5a Inhibitors  
*What you need to know*

- Inhibit viral assembly
- Pangentypic
- **Low barrier to resistance**
- Not metabolized in the liver

**Examples**
- Ledipasvir, ombitasvir, daclatasvir
- *Coming Soon*: Elbasvir, velpatasvir

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HCV Direct Acting Agents Drug Class – NS5b

<table>
<thead>
<tr>
<th>NUCLEOSIDE POLYMERASE INHIBITORS</th>
<th>NON-NUCLEOSIDE POLYMERASE INHIBITORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>High potency</td>
<td>High potency</td>
</tr>
<tr>
<td>Pangentypic</td>
<td>Pangentypic</td>
</tr>
<tr>
<td><strong>High</strong> barrier to resistance</td>
<td><strong>Low</strong> barrier to resistance</td>
</tr>
<tr>
<td><strong>Strong backbone</strong></td>
<td><strong>Weaker backbone</strong></td>
</tr>
<tr>
<td>Example: Sofosbuvir</td>
<td>Example: Dasabuvir</td>
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</tbody>
</table>
Designing a Drug Regimen

**Strong Backbone (nuc NS5b)**
- Sofosbuvir

**One Other Drug (NS5a)**
- Ledipasvir

**Weak BackBone (non-nuc NS5b)**
- Dasabuvir

**Two Other Drugs + Ribavirin**
- Paritaprevir/r + Ombitasvir + ribavirin

NS5b Inhibitor-free Regimens

**2nd Generation PI**
- Grazoprevir

**2nd Generation NS5a**
- Elbasvir

*Difficult to treat patients/prior failures
Add: Sofosbuvir +/- ribavirin*
Current Treatment Recommendations

Genotype 1

- Sofosbuvir + ledipasvir – 8-24 weeks
- Paritaprevir/r + Ombitasvir + Dasabuvir + ribavirin – 12 to 24 weeks
- Sofosbuvir + simeprevir + ribavirin – 12-to 24 weeks

WHAT’S NEW (AASLD 2015)

- Real world efficacy of 8w SOF/LDV regimen for viral load < 6 million confirmed (97% SVR-12)
- 12w of SOF/LDV + ribavirin = 24 weeks SOF/LDV
- Genotype 1b treated with Pr/O/D:
  - √ Ribavirin no longer needed for G1b cirrhosis
Genotype 2

**Sofosbuvir + ribavirin -12 weeks**

Cirrhosis
- Extend to 16 weeks

*What’s New:*

Ribavirin-intolerant option *(Not FDA-approved)*
- Sofosbuvir + daclatasvir 12 - 16 weeks

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Genotypes 4, 5 and 6

**FDA-Approved Options**

- **G4**
  - Paritaprevir/r + Ombitasvir + ribavirin 12 weeks *(no cirrhosis)*
  - Sofosbuvir + Ledipasvir 12 weeks

- **G5**
  - Sofosbuvir + Ledipasvir – 12 weeks

- **G6**
  - Sofosbuvir + Ledipasvir – 12 weeks
Genotype 3

FDA-approved options
- Sofosbuvir + ribavirin – 24 weeks
- Sofosbuvir + daclatasvir – 12 weeks

Neither option provides acceptable SVR rates for G3 cirrhosis (SVR < 70%)
Treatment Options - Cirrhosis

**FDA-Approved Options – Genotype 3**

**SOFOSBUVIR + RIBAVIRIN**
- 24 WEEKS

- Overall: 85%
- Cirrhosis Overall: 68%
- Cirrhosis Naive: 92%
- Cirrhosis Experienced: 62%

**SOFOSBUVIR + DACLATASVIR**
- 12 WEEKS

- Overall: 89%
- Cirrhosis Overall: 63%
- Cirrhosis Naive: 58%
- Cirrhosis Experienced: 69%


**AASLD 2015**

Sofosbuvir + Daclatasvir + Ribavirin for G3 Infection (Ally-3+)

- Overall: 100%
- Cirrhosis Overall: 83%
- Cirrhosis Experienced: 88%

12 Weeks
- F3: 6/6
- Cirrhosis: 31/36
- Cirrhosis - TE: 14/16

16 Weeks
- F3: 8/8
- Cirrhosis: 16/18
- Cirrhosis - TE: 12/14

AASLD 2015, Abstract LB-3
24 Weeks – SOF + DAC

European Compassionate Use Program – Daclatasvir + Sofosbuvir + ribavirin

- Ribavirin Free
- Ribavirin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ribavirin Free</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cirrhosis</td>
<td>88%</td>
<td>100%</td>
</tr>
<tr>
<td>CP-A</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>CP-B</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>CP-C</td>
<td>86%</td>
<td>100%</td>
</tr>
</tbody>
</table>

AASLD 2015, abstract 37

Other Options for G3 Cirrhosis

PEG IFN + SOFOSBUVIR + RIBAVIRIN 12 WK VS. SOFOSBUVIR + RIBAVIRIN 24 WEEKS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall Cirrhosis</th>
<th>Naïve Cirrhosis</th>
<th>Experienced Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>P+S+R 12w</td>
<td>89%</td>
<td>91%</td>
<td>86%</td>
</tr>
<tr>
<td>S+R 24w</td>
<td>78%</td>
<td>82%</td>
<td>77%</td>
</tr>
</tbody>
</table>

Interferon-free options

My Approach to G3 Infection

No cirrhosis
- Sofosbuvir + daclatasvir – 12 weeks

Cirrhosis
- Sofosbuvir + daclatasvir – 24 weeks
- Sofosbuvir + daclatasvir + ribavirin – 12 weeks

Sofosbuvir + ribavirin 24 weeks no longer recommended for G3 cirrhosis

Based on data presented at AASLD 2015 – various abstracts

Daclatasvir in G3 Infection

G3 Infection – AASLD Guidance

Treatment naïve
- No cirrhosis: sofosbuvir + Daclatasvir – 12 wk
- Cirrhosis: sofosbuvir + Daclatasvir + ribavirin – 24 weeks

Treatment experienced
- No cirrhosis: sofosbuvir + Daclatasvir – 12 wk
- Cirrhosis: Sofosbuvir + Daclatasvir + ribavirin – 24 weeks

Accessed December 1, 2015
G3 Failures to SOF + Riba

AASLD/IDSA Guidelines
1. Daclatasvir + sofosbuvir + ribavirin for 24 weeks
   ◦ Based on limited data -Daclatasvir + sofosbuvir 12 weeks – 71% SVR (n=7)
2. Sofosbuvir + PEG-IFN + ribavirin for 12 weeks

Choosing the Right Therapy
How do you choose therapy?

The decision is often made for you!

When options available, consider
- Efficacy
- Duration of therapy
- Drug-drug interactions
- Side effect profile
- Renal function

Drug-drug Interactions

Impossible to remember!
- [http://www.hep-druginteractions.org](http://www.hep-druginteractions.org)

Notable interactions
- St. John’s Wort
- Statins – varies with HCV regimen
- Acid-reducing therapy
- Amiodarone
- Ethinyl-estradiol oral contraceptives
Side Effect Profile

For the most part, DDA AE’s are similar to placebo
- Nausea
- Headache
- Fatigue

Ribavirin side effects
- Anemia
- Rash/pruritus
- Insomnia
- Irritability, anxiety, depression
- Teratogenic

Renal Function and DAA’s

**Sofosbuvir-based regimens**
- Safety unknown if GFR <30 mL/min

**Simeprevir, Daclatasvir** – no renal excretion

**Paritaprevir/r + ombitasvir + dasabuvir**
- No renal excretion
- Safe in compromised renal function
- Not tested in dialysis

**Ribavirin**
- Renal excretion
### Ribavirin Dosing in Renal Insufficiency

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>CrCL (mL/min)</th>
<th>Ribavirin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>50-80</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>MODERATE</td>
<td>30-50</td>
<td>Alternating doses 200mg and 400mg every other day</td>
</tr>
<tr>
<td>SEVERE</td>
<td>&lt;30</td>
<td>200 mg/day</td>
</tr>
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### What’s New?

- **UPCOMING NEW THERAPIES**
- **RE-TREATMENT OF FAILURES**
- **DECOMPENSATED LIVER DISEASE**
New Therapies – 2016

SOFOSBUVIR + VELPATASVIR
12 WEEKS

99% 99% 95%

Genotype 3 Cirrhosis
SVR-12

Tx naïve: 91% (n=34)
Tx Experienced: 89% (n=37)

G 1,2,4,5,6
Genotype 2
Genotype 3

n=624
n=134
n=277

Feld JJ, et al. NEJM 2015 (epub)
Foster GR, et al. NEJM 2015 (epub)

New Therapies – 2016

SOFOSBUVIR + VELPATASVIR
12 WEEKS

99% 99% 95%

G 1,2,4,5,6
Genotype 2
Genotype 3

n=624
n=134
n=277

Grazoprevir + Elbasvir
12 WEEKS

95% 92% 99% 100%

Overall
G 1a
G 1b
G 4
G 6

n=316
n=157
n=131
n=18
n=10

Feld JJ, et al. NEJM 2015 (epub)
Foster GR, et al. NEJM 2015 (epub)
Sofosbuvir Regimen Failures G1
(N55a-free regimens)

Management of prior sofosbuvir failures
- PEG-IFN + Sofosbuvir + ribavirin
- Sofosbuvir + ribavirin

Retreated with
- Sofosbuvir + ledipasvir + ribavirin 12 weeks

SVR-12: 98% (44/45)*

*The failure patient was a G3 patient that was misclassified


Is Ribavirin Needed in Sofosbuvir Failures?

14 patients, G1, prior failures to 24 weeks of sofosbuvir + ribavirin

Re-treatment: Sofosbuvir + ledipasvir 12 weeks

SVR-12: 100%

Responses included
- 1 patient with detectable S282T mutation pre-therapy
- 7 with cirrhosis

Re-treatment of Sofosbuvir/Ledipasvir Failures

Failed 8-12 weeks, re-treated with 24 weeks of ledipasvir + sofosbuvir

- 100% SVR-12 with no NS5a RAV’s
- 100% SVR-12 with NS5a RAV’s Present

<table>
<thead>
<tr>
<th>SVR-12</th>
<th>No NS5a RAV’s</th>
<th>NS5a RAV’s Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/11</td>
<td>100%</td>
<td>60%</td>
</tr>
<tr>
<td>18/30</td>
<td></td>
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</tbody>
</table>


Treatment of Genotype 1 NS5a-Experienced Patients

AASLD/IDSA Guidance

If mild liver disease
- Defer treatment until data available

Cirrhosis or need for urgent therapy
- Test for NS3 and NS5a resistance-associated variants (RAVs)

<table>
<thead>
<tr>
<th>RAV Testing Result</th>
<th>Retreatment Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>No NS5a RAVs</td>
<td>Ledipasvir/sofosbuvir + ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td>NS5a but no NS3 RAVs</td>
<td>Simeprevir + sofosbuvir + ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td>NS5a and NS3 RAVs</td>
<td>Refer to clinical trial</td>
<td></td>
</tr>
</tbody>
</table>
Decompensated Liver Disease

Current therapies approved only for compensated liver disease

Safety in decompensated cirrhotics a concern
  ◦ Avoid protease inhibitors

Efficacy of antiviral therapy is lower in advanced disease

Sofosbuvir + Ledipasvir + Ribavirin in Advanced Liver Disease (SOLAR)

Child’s Pugh B & C

Treatment arms
  ◦ Sofosbuvir + Ledipasvir + ribavirin – 12 vs. 24 weeks
  ◦ Total bilirubin <10mg/dL
  ◦ Baseline hemoglobin >10g/dL
  ◦ Ribavirin starting dose: 600mg, increased to 1,000 mg if tolerated

Efficacy in Decompensated Disease

Sofosbuvir + Ledipasvir + Ribavirin

<table>
<thead>
<tr>
<th></th>
<th>Child’s B</th>
<th>Child’s C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=30</td>
<td>87%</td>
<td>89%</td>
</tr>
<tr>
<td>n=27</td>
<td>89%</td>
<td>87%</td>
</tr>
<tr>
<td>n=22</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>n=27</td>
<td></td>
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</tr>
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</table>

12 wk 24 wk


Change in MELD Scores After Therapy

Decompensated Liver Disease - Controversies

When is it too late to treat????
- How much liver function will recover?
- Are there certain complications less likely to reverse?
- Are patients going to remain in “transplant list purgatory” forever?
- Patients no longer eligible for HCV (+) organs

Should we allow patients to be transplanted, then treat?

Post Liver Transplantation

<table>
<thead>
<tr>
<th>Condition</th>
<th>12 wks</th>
<th>24 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>96%</td>
<td>98%</td>
</tr>
<tr>
<td>Child’s A</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>Child’s B</td>
<td>85%</td>
<td>88%</td>
</tr>
<tr>
<td>Child’s C</td>
<td>60%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Back to Reality...

Insurance approval is difficult
- Getting better
- Most require fibrosis thresholds
- Cumbersome and time consuming
- Temptation to not even try....

Resist the Temptation Not to Try to Get Approval
- Liability issues
  - Biopsy may have underestimated fibrosis
  - Patient may develop extra-hepatic complications of HCV
- Approval rules change frequently – you will be the last one to know
- Appealing a denial may get your patient approved

Having a denial letter in the medical record will help you when your patient develops unexpected complications of untreated HCV!
Take Home Points

1. HCV is a curable illness
2. New treatment options
   - Safe
   - Effective
   - Simple
3. Every infected patient should be considered a candidate for therapy
4. Visit the AASLD/IDSA guidelines frequently to keep up to date