Developments in the Treatment of Hepatitis C: A New Era

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October 17, 2014

Pharmacist Objectives
- Summarize the results of clinical trials for the newest medications approved for hepatitis C treatment and where these medications fit into treatment decisions.
- Discuss how to develop a clinical pharmacist program for the treatment of hepatitis C and become an integral part of the treatment team.
- Apply knowledge of the medication options for hepatitis C to patient cases.

Technician Objectives
- Summarize the major side effects for the newest medications approved for hepatitis C treatment and why patients may benefit more from these medications.
- Discuss how a pharmacist or technician may help in the treatment of patients with hepatitis C.
- Apply knowledge of the medication options for hepatitis C to patient cases.

Pre-Assessment Questions
- Interferon is no longer needed to treat Hepatitis C in some patient situations.
  - True
  - False

- Sofosbuvir can be used to treat patients co-infected with hepatitis C & HIV.
  - True
  - False

Hepatitis C Virus (HCV)
- 3.2 million infected in US
- Most common reason for liver transplant
- 75-85% develop chronic infection
- Of every 100 persons with chronic infection, approximately:
  - 1-5 will die from liver cancer or cirrhosis
  - 5-20 develop cirrhosis
  - 60-70 develop chronic liver disease

Assuming a patient has Hepatitis C, which is the most likely genotype he’s infected with?
- Genotype 1
- Genotype 2
- Genotype 3
- Genotype 4

http://www.cdc.gov/hepatitis/C/index.htm
What percentage of patients are unaware they have Hepatitis C?

- 25%
- 50%
- 60%
- 75%

Interpreting Hepatitis C Test Results

<table>
<thead>
<tr>
<th>Anti-HCV</th>
<th>HCV RNA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>No current infection No prior HCV exposure</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Repeat HCV RNA (false +?) Prior HCV exposure No current HCV infection Spontaneous clearance or successful treatment</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Chronic HCV infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Early, acute infection Chronic in immuno-suppressed patients</td>
</tr>
</tbody>
</table>

Measurement of Response to Treatment

- **Rapid Virologic Response (RVR)**
  - Undetectable RNA at week 4 of treatment
- **Extended Rapid Virologic Response (eRVR)**
  - Undetectable RNA at weeks 4-12 of treatment
- **Sustained Virologic Response (SVR)**
  - Undetectable RNA after treatment complete
- **Partial Response**
  - At least $2 \log_{10}$ decrease in RNA, but not undetectable
  - Example: $1,000,000 \rightarrow <10,000$

Treatment Options

Before 2011:

Ribavirin (RBV)+ Peginterferon alfa (PEG)

Limitations of RBV + PEG

- Many do not achieve SVR
- Drug interactions limit use
- Pregnancy Category X (RBV)
- Expensive
- Resistance may occur
- Response rates low in cirrhosis
- Limited efficacy other than genotype 1
- Extensive side effects
Side Effects of RBV + PEG

- Flu-like symptoms
- Anemia
- Neutropenia
- Thrombocytopenia
- ↑ Blood sugars
- Hypo- or Hyperthyroidism
- ↑ LFTs
- Hair loss
- Rash
- Depression
- Fatigue
- Irritability/mania
- Insomnia
- Dyspnea
- Nonproductive cough
- Worsening autoimmune disorders
- Hypo- or Hyperthyroidism
- ↑ LFTs
- Hair loss
- Rash
- Depression
- Fatigue
- Irritability/mania
- Insomnia
- Dyspnea
- Nonproductive cough
- Worsening autoimmune disorders

First-Generation Protease Inhibitors (PI)

- Boceprevir (Victrelis®), Telaprevir (Incivek®)
- Only effective against genotype 1
- Response rate: 63-80%
- Mechanism: inhibit NS3/NS4A protease
- TID (boceprevir) or BID (telaprevir) with meals
  - Combination therapy with RBV + PEG
  - 24-48 week duration

First-Generation PI

- Significant side effects
  - Rash, fatigue, anemia, nausea, headache, dysgeusia
- Drug interactions
  - Strong inhibitors of CYP3A
  - P-glycoprotein substrates & inhibitors
  - Decrease oral contraceptive efficacy
- Telaprevir to be removed from US market in October 2014

Simeprevir (Olysio®)

- Second-generation PI
- Genotype 1
  - Test for Q80K polymorphism in genotype 1a → less effective
- Dosing: 150 mg po daily with food
  - Not if Clcr<30 mL/min or dialysis
- Can be used in patients co-infected with HIV

Before 2011

May 2011: Boceprevir, Telaprevir

November 2013: Simeprevir

Before 2011

May 2011
Simeprevir (Olysio®)

- Side effects
  - Rash, photosensitivity, itching, nausea, fatigue, headache
- Contains sulfonamide moiety
- Less drug interactions than first-generation PI
  - Weak inhibitor of CYP3A4, CYP1A2, P-glycoprotein

QUEST-1 & QUEST-2 Trials

- Previously untreated patients, genotype 1

Treatment Groups:
- Simeprevir + RBV + PEG for 12 weeks, then
  - If eRVR → RBV + PEG for 12 weeks
  - If not → RBV + PEG for 36 weeks
- Placebo + RBV + PEG x 12 weeks, then RBV + PEG x 36 weeks

<table>
<thead>
<tr>
<th>Trial</th>
<th>Rate of SVR at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Group</td>
</tr>
<tr>
<td>QUEST-1</td>
<td>n=264</td>
</tr>
<tr>
<td></td>
<td>80% Overall</td>
</tr>
<tr>
<td></td>
<td>71% Genotype 1a</td>
</tr>
<tr>
<td></td>
<td>52% with Q80K</td>
</tr>
<tr>
<td></td>
<td>85% without Q80K</td>
</tr>
<tr>
<td></td>
<td>90% Genotype 1b</td>
</tr>
<tr>
<td>QUEST-2</td>
<td>n=257</td>
</tr>
<tr>
<td></td>
<td>81% Overall</td>
</tr>
<tr>
<td></td>
<td>80% Genotype 1a</td>
</tr>
<tr>
<td></td>
<td>75% with Q80K</td>
</tr>
<tr>
<td></td>
<td>82% without Q80K</td>
</tr>
<tr>
<td></td>
<td>82% Genotype 1b</td>
</tr>
</tbody>
</table>

PROMISE Trial

- Prior treatment & relapse, genotype 1

Treatment Groups:
- Simeprevir + RBV + PEG x 12 weeks
  - If eRVR → RBV + PEG x 12 weeks
  - If not → RBV + PEG for 36 weeks
- Placebo + RBV + PEG x 12 weeks, then RBV + PEG x 36 weeks

<table>
<thead>
<tr>
<th>Rate of SVR at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Group (n=260)</td>
</tr>
<tr>
<td>79% Overall</td>
</tr>
<tr>
<td>70% Genotype 1a</td>
</tr>
<tr>
<td>47% with Q80K</td>
</tr>
<tr>
<td>78% without Q80K</td>
</tr>
<tr>
<td>86% Genotype 1b</td>
</tr>
</tbody>
</table>

ASPIRE Trial

- Previous treatment with relapse, partial response, or null response (phase 2 trial)
- Genotype 1

Treatment Groups:
- Simeprevir + RBV + PEG x 12 weeks, then 36 weeks RBV + PEG
- Simeprevir + RBV + PEG x 24 weeks, then 24 weeks RBV + PEG
- Simeprevir + RBV + PEG x 48 weeks
- Placebo + RBV + PEG x 48 weeks
**Simeprevir 150 mg + RBV + PEG (12 weeks), then RBV + PEG (36 weeks)**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Rate of SVR at 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simeprevir *</td>
</tr>
<tr>
<td>Prior Relapsers</td>
<td>76.9% (n=26)</td>
</tr>
<tr>
<td>Prior Partial Responder</td>
<td>65.2% (n=23)</td>
</tr>
<tr>
<td>Prior Null Responders</td>
<td>52.9% (n=17)</td>
</tr>
<tr>
<td>Overall</td>
<td>66.7% (n=66)</td>
</tr>
</tbody>
</table>

*Gastroenterology. 2014;146:430-41.*

**Sofosbuvir (Sovaldi®)**
- **Mechanism:** Nucleotide analog NS5B polymerase inhibitor
- **Dose:** 400 mg po daily
  - Avoid if Clcr<30 mL/min or dialysis
- **Can be used in patients co-infected with HIV**

**NEUTRINO Trial**
- Previously untreated, open-label
- Genotype 1, 4, 5, 6
  - 89% genotype 1

**Rate of SVR at 12 weeks**
- Sofosbuvir + RBV + PEG x 12 weeks (n=327)
  - 90% Overall
  - 92% Genotype 1a
  - 82% Genotype 1b

**FISSION Trial**
- Previously untreated, noninferiority trial
- Genotype 2 or 3

**Rate of SVR at 12 weeks**
- Sofosbuvir + RBV x 12 weeks (n=253)
  - 67% Overall
  - 97% Genotype 2
  - 56% Genotype 3
- PEG + RBV x 24 weeks (n=243)
  - 67% Overall
  - 78% Genotype 2
  - 63% Genotype 3

**Sofosbuvir (Sovaldi®)**
- **Side Effects**
  - Fatigue, headache, nausea, insomnia, anemia, rash, arthralgia
- **Drug interactions**
  - P-glycoprotein substrate
  - Avoid modafinil, oxcarbazepine, rifabutin, rifapentine

**Before 2011**

**Nov 2013**

**May 2011**

**December 2013: Sofosbuvir**

**Gastroenterology. 2014;146:430-41.**

**Sofosbuvir prescribing information. Pharmacist's Letter/Prescriber's Letter. #300204. February 2014.**

**NEUTRINO Trial**

**FISSION Trial**

**Gastroenterology. 2014;146:430-41.**

**N Engl J Med. 2013;368:1878-87.**

**N Engl J Med. 2013;368:1878-87.**

**N Engl J Med. 2013;368:1878-87.**
**POSITRON Trial**
- Interferon intolerant, genotype 2 or 3
  - Previously stopped due to side effects
  - Concurrent medical condition precluding use
  - Decided against use

<table>
<thead>
<tr>
<th>Rate of SVR at 12 weeks</th>
<th>Sofosbuvir + RBV x 12 weeks (n=207)</th>
<th>Placebo x 12 weeks (n=71)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>78% Overall</td>
<td>0%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>93% Genotype 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61% Genotype 3</td>
<td></td>
<td></td>
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</tbody>
</table>

**FUSION Trial**
- Interferon failure
  - Nonresponse or relapse
  - Genotype 2 or 3

<table>
<thead>
<tr>
<th>Rate of SVR at 12 weeks</th>
<th>Sofosbuvir + RBV x 12 weeks (n=100)</th>
<th>Sofosbuvir + RBV x 16 weeks (n=95)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% Overall</td>
<td>73% Overall</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>86% Genotype 2</td>
<td>94% Genotype 2</td>
<td>62% Genotype 3</td>
<td></td>
</tr>
<tr>
<td>30% Genotype 3</td>
<td></td>
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</tbody>
</table>

**VALENCE Trial**
- Treatment naïve or experienced
- Genotype 2 or 3

<table>
<thead>
<tr>
<th>Rate of SVR at 12 weeks</th>
<th>Sofosbuvir + RBV x 12 weeks (genotype 2) (n=73)</th>
<th>Sofosbuvir + RBV x 24 weeks (genotype 3) (n=250)</th>
<th>Placebo + RBV x 12 weeks (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>93%</td>
<td>85%</td>
<td>0%</td>
<td></td>
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</tbody>
</table>

**COSMOS Trial**
- Genotype 1
- Two cohorts:
  1. Prior nonresponders to RBV + PEG with Metavir F0-F2
  2. Prior nonresponders to RBV + PEG or treatment naïve with Metavir F3-F4
- Treatment Groups:
  - Simeprevir + Sofosbuvir + RBV x 24 weeks
  - Simeprevir + Sofosbuvir x 24 weeks
  - Simeprevir + Sofosbuvir + RBV x 12 weeks
  - Simeprevir + Sofosbuvir x 12 weeks

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Rate of SVR at 12 weeks</th>
<th>Cohort 1 (F0-F2)</th>
<th>Cohort 2 (F3-F4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ RBV 24 weeks</td>
<td>79% (n=24)</td>
<td>93% (n=30)</td>
<td></td>
</tr>
<tr>
<td>- RBV 24 weeks</td>
<td>93% (n=15)</td>
<td>100% (n=16)</td>
<td></td>
</tr>
<tr>
<td>+ RBV 12 weeks</td>
<td>96% (n=27)</td>
<td>93% (n=27)</td>
<td></td>
</tr>
<tr>
<td>- RBV 12 weeks</td>
<td>93% (n=14)</td>
<td>93% (n=14)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>90% (n=80)</td>
<td>94% (n=87)</td>
<td></td>
</tr>
</tbody>
</table>

**Dosing Regimens**
**Simeprevir**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Naïve or Prior Relapers* (genotype 1)</td>
<td>Simeprevir + RBV + PEG x 12 weeks, then RBV + PEG x 12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Prior Partial Responders or Nonresponders* (genotype 1)</td>
<td>Simeprevir + RBV + PEG x 12 weeks, then RBV + PEG x 36 weeks</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Treatment Naïve (genotype 4)</td>
<td>Simeprevir + RBV + PEG x 12 weeks, then RBV + PEG x 12-36 weeks</td>
<td>24-36 weeks</td>
</tr>
</tbody>
</table>

*No PI in previous treatment

**Sofosbuvir: Treatment Naïve**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sofosbuvir + RBV + PEG</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + Simeprevir +/- RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td>2</td>
<td>Sofosbuvir + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Sofosbuvir + RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + RBV + PEG</td>
<td>12 weeks</td>
</tr>
<tr>
<td>4</td>
<td>Sofosbuvir + RBV + PEG</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td>5 or 6</td>
<td>Sofosbuvir + RBV + PEG</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

**Sofosbuvir: Relapsers**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sofosbuvir x 12 weeks + RBV/PEG x 12-24 weeks (with or without previous PI)</td>
<td>12-24 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + Simeprevir +/- RBV (without previous PI)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>2</td>
<td>Sofosbuvir + RBV</td>
<td>12-16 weeks</td>
</tr>
<tr>
<td>3 or 4</td>
<td>Sofosbuvir + RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + RBV + PEG</td>
<td>12 weeks</td>
</tr>
<tr>
<td>5 or 6</td>
<td>Sofosbuvir + RBV + PEG</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

**Simeprevir in HIV Co-Infection**

- Used only in combination with sofosbuvir +/- RBV
- Genotype 1 only
- Avoid any antiretrovirals that would interact
- Options that can be used:
  - Raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir

**Future Options?**

Before 2011

Nov 2013

May 2011

Dec 2013

Getting Involved: Ambulatory Clinic Setting

Our Involvement
- Review referred cases
  - Genotype, viral load, liver function
- Arrange for screening of patients
  - Severity of depression
  - Any potential issues for nonadherence
- Baseline laboratory monitoring

Baseline Laboratory Tests
- HIV
- Hepatitis B
- Hepatitis A
- CBC
- Chem-7
- LFTs
- TSH
- EKG if baseline cardiac disease
- HCV RNA levels
- Genotype
- Q80K polymorphism in genotype 1a if considering simeprevir
- Pregnancy test

Our Involvement
- Recommendations for treatment
  - Education on medications & adherence
    - 2 methods of contraception
  - Insurance authorization and/or patient assistance programs

Cost
- Ribavirin 600 mg bid
  - $21,016.66 for 28 weeks
- Peginterferon alfa-2a
  - $21,595.56 for 28 weeks
- Simeprevir 150 mg
  - $66,360 for 12 weeks
- Sofosbuvir 400 mg
  - $84,000 for 12 weeks

Our Involvement
- Shipment of medications to clinic/patient
- Follow with patient throughout treatment
  - Adherence issues
  - Side effects
- Post-treatment lab work
Follow-Up Monitoring
- CBC, Chem 7, LFTs
  - At weeks 1, 2, 5, 6, and 8.
  - Then q 4-6 weeks as indicated
- HCV RNA levels
  - Weeks 4 & 12
  - 12 weeks after treatment
- Pregnancy test monthly during treatment + 6 months after stopped
- TSH q 12 weeks

Patient Cases

Case #1
- 57 yo M recently diagnosed with Hepatitis C
- Labs:
  - Genotype: 1a, Q80K positive
  - HCV RNA = 1,365,000
  - LFTs showed elevated ALT
  - Other labs normal
- Other PMH: Hyperlipidemia, Hypertension
- Medications: Atorvastatin 20 mg QHS, Lisinopril 20 mg daily

Which regimen would be recommended first line?
- Sofosbuvir + Simeprevir + RBV
- Sofosbuvir + RBV + PEG
- Simeprevir + RBV + PEG
- RBV + PEG

What would be the recommended duration of treatment?
- 8 weeks
- 12 weeks
- 24 weeks
- 48 weeks

If his starting HCV RNA level was 1,365,000, what would be considered SVR?
- <13,650
- <1,365
- <136
- Undetectable
Case #2
- 32 yo F previously treated with telaprevir + PEG + RBV, but did not tolerate and stopped. Interested in retreatment.
- Labs:
  - Genotype 1b
  - HCV RNA = 25,564,000
  - LFTs and other labs normal
- Other PMH: depression, chronic back pain
- Medications: Ortho Tri-Cyclen Lo daily, Fluoxetine 40mg daily, Oxycodone IR 5mg QID pm

Which medication is least appropriate for this patient?
- Sofosbuvir
- RBV
- Simeprevir
- PEG

The following regimen is appropriate for this patient:
Sofosbuvir + RBV + PEG
- True
- False

What counseling points must be communicated to this patient?
- Need for 2 forms of contraception
- Need for pregnancy tests monthly and for 6 months after discontinuing therapy
- Need to take medications without missing doses
- All of the above

Case #3
- 45 yo M recently diagnosed with Hepatitis C
- Labs:
  - Genotype 2, HCV RNA 984,000
  - Other labs normal
- Other PMH: HIV (CD4 324)
- Medications: None currently
  - Also being evaluated for HIV treatment

Which medication is not an option for treatment?
- Sofosbuvir
- RBV
- Simeprevir
- PEG
Key Points
- Hepatitis C can be cured but at a huge cost.
- Newer regimens are better tolerated & require a shorter treatment duration.
- Many new drugs are in the pipeline & we will likely see many new medications and more interferon-free regimens in the future.

Post-Assessment Questions
- Interferon is no longer needed to treat Hepatitis C in some patient situations.
  - True
  - False
- Sofosbuvir can be used to treat patients co-infected with hepatitis C & HIV.
  - True
  - False

References
- Lawitz E, Sulkowski MS, Ghalib R et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 infection in non-responders to pegylated interferon and ribavirin: the COSMOS randomised study. Lancet. 2014;384(9949):1649-58.