Hepatitis C Infection
Treatment Revolution

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Disclosures

I have no relevant financial or non financial relationships to disclose in relation to the content of this presentation

Objectives

1. Review hepatitis and acute viral hepatitis
2. Discuss the epidemiology, etiology, pathophysiology and risk factors of Hepatitis C infection
3. Describe the clinical features and presentation of Hepatitis C infection
Objectives

4. Explain the diagnostic considerations for Hepatitis C infection
5. Evaluate the goals of therapy, nonpharmacologic and pharmacologic treatment of Hepatitis C infection
6. Apply the guidelines and treatment costs of Hepatitis C infection when implementing therapy

Abbreviations

- DCV – Daclatasvir
- SOF – Sofosbuvir
- SVR 12 – Sustained virologic response 12 weeks post treatment
- RBV – Ribavirin
- LDV – Ledipasvir

Abbreviations

- SMV – Simeprevir
- PEG-IFN – Peginterferon alfa 2a
- ALT – Alanine aminotransferase
- AASLD – American Association for the Study of Liver Diseases
- IDSA – Infectious Disease Society of America
Self-Assessment Questions

Question 1

True or False: Hepatitis C infection is preventable with a vaccine

Question 2

True or False: Most persons are asymptomatic when first contracting hepatitis C infection

Question 3
True or False: The most common side effect of Harvoni® (ledipasvir and sofosbuvir) is myelosuppression.

What is Hepatitis? ¹

- **Hepatitis:**
  - Inflammation of the liver

- **Acute viral hepatitis:**
  - A systemic infection affecting the liver predominantly

What is Hepatitis? ¹

5 Main Hepatitis Viruses

- **Hepatitis A virus (HAV)**
- **Hepatitis B virus (HBV)**
- **Hepatitis C virus (HCV)**
- **Hepatitis D virus (HDV)**
- **Hepatitis E virus (HEV)**
Hepatitis C Virus

Epidemiology

- 2.7 million persons are chronically infected in the United States
- Leading cause of chronic liver disease and transplantation
- Between 2010 and 2014, more than 190,000 deaths from HCV-related disease are expected

Etiology

- Type: Single stranded Ribonucleic acid
- Genus: Hepacivirus
- Family: Flavivirdae
- 6 major genotypes: 1, 2, 3, 4, 5 and 6
- >50 subtypes: a, b, c, etc.
Risk factors

- **Risk behaviors**
  - Intravenous and intranasal drug use
- **Risk exposures**
  - Long-term hemodialysis
  - Getting a tattoo
  - Occupational exposure
  - Children born to HCV-infected mothers
- **Other medical conditions**
  - HIV infection
  - Solid organ donors

Clinical presentation

- Anorexia
- Vague abdominal discomfort
- Nausea
- Vomiting
- Fatigue
- Fever
- Jaundice
- Clay – color stool
- Elevated LFTS

Clinical Features

- **Incubation period**
  - 15 – 160 days
- **Type of infection**
  - Acute ➔ Chronic
- **Major organ affected**
  - Liver
- **Principal age distribution**
  - Adults
- **Lifelong protection**
  - No
Time Course of Progression

Diagnostic Considerations

Laboratory Testing

• Serologic assays
  • Detect Anti-HCV antibodies

• Molecular assays
  • Detect HCV RNA levels

• Genotype assays
  • Differentiate between genotypes

Assessment of Fibrosis Stage

• History and Physical Examination
• Basic Laboratory Testing

Interpretation of HCV Assays

<table>
<thead>
<tr>
<th>Anti-HCV Antibodies</th>
<th>HCV RNA Levels</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>Acute or chronic HCV infection</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>Resolution of HCV infection</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>Early acute HCV infection</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>Absence of HCV infection</td>
</tr>
</tbody>
</table>
Treatment

Goals of Therapy

Reduce all-cause mortality
Eradicate the infection
Prevent the development of complications
Achieve histological improvement

When and In Whom to Initiate HCV Therapy?

When
• Early in the course of the infection before the development of severe liver disease and other complications

Whom
• All patients, except those with short life expectancies that cannot be remediated by treatment, by transplantation, or by other directed therapies
Nonpharmacologic Treatment

**General**
- Avoid sharing toothbrushes
- Avoid sharing shaving equipment
- Do not donate blood

**Alcohol abstinence/cessation**

**Vaccinations**
- Hepatitis A and hepatitis B vaccines
- There is no hepatitis C vaccine!

Pharmacologic Treatment

- Daclatasvir
- Ledipasvir/Sofosbuvir
- Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir
- Ombitasvir/Paritaprevir/Ritonavir
- Ribavirin
- Peginterferon alfa-2

Daclatasvir (Daklinza®)

**Therapeutic Class**
- NS5A inhibitor

**Contraindications**
- Strong inducers of CYP3A including: phenytoin, rifampin, carbamazepine, and St. John’s Wort
**Daclatasvir (Daklinza®)**

**Dosing**

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Tablets:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 3</td>
<td>30 mg &amp; 60 mg</td>
</tr>
<tr>
<td></td>
<td>60 mg daily</td>
</tr>
</tbody>
</table>

**Pricing**

| 30 mg & 60 mg (28) | $25200.00 |

**Special Population**

- No renal or hepatic adjustment necessary

**Administration**

- Administer with or without food

**ALLY-3 Study**

- **Study Design**
  - Open-label, two-cohort phase-III, multicenter study of a 12 week regimen of DCV plus SOF in genotype 3 infection

- **Patient population**
  - Genotype 3, treatment-naïve and experienced patients with or without cirrhosis

- **Primary endpoint**
  - SVR12
### Daclatasvir (Daklinza®) 11

**ALLY-3 Study**

- **Results**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No cirrhosis</td>
<td>Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Treatment-naive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>97% (73/75)</td>
<td>58% (11/19)</td>
<td></td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>94% (32/34)</td>
<td>69% (9/13)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>63% (20/32)</td>
<td>58% (11/19)</td>
<td></td>
</tr>
</tbody>
</table>

### Daclatasvir (Daklinza®) 12

**European Compassionate Use Program**

- **Study Design**
  - 24 week regimen of DCV+SOF versus DCV+SOF+RBV in genotype 3 infection

- **Patient population**
  - Genotype 3, treatment-naive and experienced patients with and without cirrhosis

- **Primary endpoint**
  - SVR12

### Daclatasvir (Daklinza®) 12

**European Compassionate Use Program**

- **Results (Interim Analysis)**

<table>
<thead>
<tr>
<th></th>
<th>DCV + SOF</th>
<th>DCV + SOF + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>88% (42/49)</td>
<td>88% (37/42)</td>
</tr>
</tbody>
</table>
Ledipasvir/Sofosbuvir (Harvoni®)

**Therapeutic Class**
- Ledipasvir: NS5A inhibitor
- Sofosbuvir (Sovaldi®): NS5B polymerase inhibitor

**Pharmacokinetics**
- Sofosbuvir → Prodrug

**Core**
- E1
- E2
- Ns2
- Ns3
- Ns4A
- Ns4B
- Ns5A
- Ns5B

**Dosing**

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Tablets: 90 mg (L) &amp; 400 mg (S)</th>
</tr>
</thead>
</table>

**Genotype 1**
- 1 tablet daily

**Pricing**
- 90mg/400 mg (28) $37,800.00

**Drug-drug Interaction**
- Drugs that increase gastric pH
  - Digoxin, HIV antiretroviral, rosvastatin

**Administration**
- Antacids: Separate by 4 hours
- H2RAs: Administer with or separate by 12 hours
- PPIs: Administer under fasting conditions
ION-1 Study

- Study Design
  - Open-label, multicenter study in which patients were randomly assigned in a 1:1:1:1 ratio of the 4 regimens: LDV-SOF for 12 or 24 weeks, LDV-SOF+RBV for 12 or 24 weeks

- Patient population
  - Genotype 1, treatment-naive patients with or without cirrhosis

- Primary endpoint
  - SVR12

ION-1 Study

- Results

<table>
<thead>
<tr>
<th>12 week Regimen</th>
<th>24 week Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV-SOF</td>
<td>LDV-SOF</td>
</tr>
<tr>
<td>99% (211/214)</td>
<td>99% (215/217)</td>
</tr>
<tr>
<td>LDV-SOF+RBV</td>
<td>LDV-SOF+RBV</td>
</tr>
<tr>
<td>97% (211/217)</td>
<td>98% (212/217)</td>
</tr>
</tbody>
</table>

Ledipasvir/Sofosbuvir (Harvoni®)

- Therapeutic Class
  - Ombitasvir: HCV NS5A inhibitor
  - Paritaprevir: HCV NS3/4A protease inhibitor
  - Dasabuvir: HCV RNA polymerase inhibitor
  - Ritonavir: Potent CYP3A inhibitor that ↑ paritaprevir levels

- Contraindications
  - Moderate to severe hepatic impairment (Child-Pugh B and C)
  - Moderate to strong inducers of CYP3A4
  - Strong inducers and inhibitors of CYP 2C8
Dosing

Genotype 1
- 2 ombitasvir, paritaprevir, ritonavir tablet once daily and 1 dasabuvir tablet twice daily

Pricing

<table>
<thead>
<tr>
<th>Dose</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5-75-50 &amp; 250 mg (112)</td>
<td>$33,327.60</td>
</tr>
</tbody>
</table>

Ombitasvir/Paritaprevir/Ritonavir; Dasabuvir (Viekira Pak®)

**PEARL-IV Study**

- **Study Design**
  - Double-blinded, multicenter study in which patients were assigned in a 1:2 ratio (genotype 1a study) or a 1:1 ratio (genotype 1b study) to receive Viekira Pak ± ribavirin

- **Patient population**
  - Genotype 1, treatment-naive patients without cirrhosis

- **Primary endpoints**
  - SVR12
  - Non-inferiority (margin -10.5%) of SVR12 in each study group

**Results**

<table>
<thead>
<tr>
<th>Genotype 1a</th>
<th>Genotype 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viekira Pak+RBV</td>
<td>Viekira Pak</td>
</tr>
<tr>
<td>97% (87/100)</td>
<td>90% (185/205)</td>
</tr>
</tbody>
</table>

Non-inferior margin: -10.5

- 95% CI, -12.0 to -1.5: Not non-inferior
- 95% CI, -2.1 to 1.1: Non-inferior

(15)
**Simeprevir (Olysio®)**

**Therapeutic Class**
- HCV NS3/4A protease inhibitor

**Drug-drug Interactions**
- Substrate of CYP 3A4 (major) and P-glycoprotein transporter
- Inhibited by amiodarone, azithromycin, verapamil and ritonavir

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**Dosing**

- **Dosage Form**
  - Capsule: 150 mg

- **Genotype**
  - 1 or 4

- **Pricing**
  - 150 mg (28) = $26,544.00

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**Special Population**

- Not studied in patients with CrCl ≤ 30 mL/min or ESRD

**Administration**

- Administer with food
OPTIMIST-1 Study

**Study Design**
- Phase 3, multicenter, randomized, open-label study comparing the efficacy of a 12 week vs 8 week treatment regimen of SMV + SOF

**Patient Population**
- Genotype 1, treatment – naïve and experienced patients without cirrhosis

**Primary endpoint**
- SVR12

**Results**

<table>
<thead>
<tr>
<th>Regimen Type</th>
<th>Treatment-naïve (12 week)</th>
<th>Treatment-experienced (12 week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 week Regimen</td>
<td>97% (112/115)</td>
<td>95% (38/40)</td>
</tr>
<tr>
<td>8 week Regimen</td>
<td>83% (128/155)</td>
<td></td>
</tr>
</tbody>
</table>

**OPTIMIST-2 Study**

**Study Design**
- Phase 3, randomized, open-label study using SMV + SOF for 12 weeks in patients with compensated cirrhosis

**Patient Population**
- Genotype 1, treatment – naïve and experienced patients with cirrhosis

**Primary endpoint**
- SVR12
### Simeprevir (Olysio®)

**OPTIMIST-2 Study**

- **Results**
  - **All patients** 83% (86/103)
  - **Genotype 1a** 83% (60/72)
  - **Genotype 1b** 84% (26/31)

<table>
<thead>
<tr>
<th>With Q80K</th>
<th>Without Q80K</th>
</tr>
</thead>
<tbody>
<tr>
<td>74% (25/34)</td>
<td>92% (35/38)</td>
</tr>
</tbody>
</table>

### Ribavirin (Copegus®)

- **Mechanism of Action**
  - Nucleoside analog that is incorporated into virus

- **Contraindications**
  - Pregnant women and men whose female partners are pregnant
  - Hemoglobinopathies
  - Administration with didanosine

### Dosing

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Genotype 1 &amp; 4</th>
<th>Genotype 2 &amp; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg tablets</td>
<td>&lt;75 kg = 1000 mg daily</td>
<td>75 kg = 1200 mg daily</td>
</tr>
<tr>
<td>Genotype 1 &amp; 4</td>
<td>800 mg daily</td>
<td></td>
</tr>
</tbody>
</table>

### Pricing

| 200 mg (168) | $1,390.00 |

[http://www.hepatitis.uw.edu](http://www.hepatitis.uw.edu)
**Ribavirin (Copegus®)**

**Special Population**
- Approved in adults and children ≥ 2 years
- Dose adjustment in renal impairment

**Administration**
- Administer with food

**Mechanism of Action**
- Inhibits transcription, translation, protein processing and virus maturation

**Contraindications**
- Current psychosis
- Severe Depression
- Thrombocytopenia
- Symptomatic heart disease
- Decompensated liver disease
- Uncontrolled seizures

---

**Peginterferon Alfa – 2a (Pegasys®)**

**Dosing**

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Dosage Form</th>
<th>Pricing</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 mcg per 0.5 mL or 1 mL</td>
<td>180 mcg subcutaneous once weekly</td>
<td>$1,039.83</td>
</tr>
</tbody>
</table>

---

**Peginterferon Alfa – 2a (Pegasys®)**

**Dosing**

**Pricing**

- 180 mcg (0.5 mL) $1,039.83
### Peginterferon Alfa – 2a (Pegasys®)

**Special Population**
- Approved in adults and children ≥ 5 years
- CrCl < 30 mL/min & ESRD: Decrease dosage from 180 mcg to 135 mcg once weekly

**Administration**
- Administer in the abdomen or thigh, and rotate injection site

---

### Side Effects Overview

<table>
<thead>
<tr>
<th>Daklinza® 10</th>
<th>Harvoni® 13</th>
<th>Viekira Pak® 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Insomnia</td>
<td>Nausea</td>
</tr>
<tr>
<td>Nausea</td>
<td>Diarrhea</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Nausea</td>
<td>Skin reactions</td>
</tr>
<tr>
<td>Headache</td>
<td>Headache</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Olysio® 17</th>
<th>Copegus® 20</th>
<th>Pegasys® 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>Anemia</td>
<td>Thyroid suppression</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Alopecia</td>
<td>Pain</td>
</tr>
<tr>
<td>Nausea</td>
<td>Neutropenia</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Leukopenia</td>
<td>Depression</td>
</tr>
<tr>
<td>Skin rash</td>
<td>Nausea</td>
<td>Myalgia</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Weakness</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Myelosuppression</td>
</tr>
</tbody>
</table>
AASLD/IDSA Guideline: 2014

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended</th>
<th>Genotype</th>
<th>Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IFN eligible:</td>
<td>2</td>
<td>SOF + RBV x 12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + PEG/RBV x 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IFN ineligible:</td>
<td>3</td>
<td>SOF + RBV x 24 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + SMV ± RBV x 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>IFN eligible:</td>
<td>5</td>
<td>SOF + PEG/RBV x 12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + PEG/RBV x 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IFN ineligible:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOF + SMV ± RBV x 24 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AASLD/IDSA Guideline: 2015

Initial Treatment of Chronic HCV Infection

- Genotype 1
- Genotype 2
- Genotype 3
- Genotype 4
- Genotype 5 or 6
### Recommended Regimen

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Without Cirrhosis</th>
<th>Cirrhosis</th>
<th>Genotype 5 or 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
<td><strong>Recommended Regimen</strong></td>
<td><strong>Recommended Regimen</strong></td>
<td><strong>Recommended Regimen</strong></td>
</tr>
<tr>
<td><strong>Without Cirrhosis</strong></td>
<td><strong>DCV + SOF</strong></td>
<td><strong>DCV + SOF ± RBV</strong></td>
<td><strong>DCV + SOF</strong></td>
</tr>
<tr>
<td></td>
<td><strong>12 weeks</strong></td>
<td><strong>24 weeks</strong></td>
<td><strong>12 weeks</strong></td>
</tr>
<tr>
<td><strong>LDV-SOF</strong></td>
<td><strong>12 weeks</strong></td>
<td><strong>12 weeks</strong></td>
<td><strong>12 weeks</strong></td>
</tr>
<tr>
<td><strong>Viekira Pak + RBV</strong></td>
<td><strong>12 weeks</strong></td>
<td><strong>24 weeks</strong></td>
<td><strong>12 weeks</strong></td>
</tr>
<tr>
<td><strong>SMV + SOF</strong></td>
<td><strong>12 weeks</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Genotype 1

- Extending treatment to 16 weeks is recommended in patients with cirrhosis.

### Genotype 2

### Genotype 3

### Genotype 4

### Genotype 5 or 6

*Without Q80K polymorphism*
<table>
<thead>
<tr>
<th>Recommended Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without Cirrhosis</strong></td>
<td></td>
</tr>
<tr>
<td>DCV + SOF</td>
<td>12 weeks</td>
</tr>
<tr>
<td>SOF + RBV + PEG-IFN</td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
</tr>
<tr>
<td>DCV + SOF ± RBV</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

*Regimen does not include twice daily dasabuvir.*
Monitoring

Monitoring Parameters

- Quantitative HCV viral load testing
- CBC
- GFR
- Hepatic function panel
- TSH
- Physical examination
- Vitals signs
- Pregnancy testing and counseling
- Adverse events and Contraindications

Self-Assessment Questions
True or False: Hepatitis C infection is preventable with a vaccine
✓ Answer: False

True or False: Most persons are asymptomatic when first contracting hepatitis C infection
✓ Answer: True

True or False: The most common side effect of Harvoni® (ledipasvir and sofosbuvir) is myelosuppression
✓ Answer: False
References


9. Terrault NA, Chopra S. Diagnosis and evaluation of chronic hepatitis C virus infection. Marion, DW. Diaphragmatic pacing. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on November 25, 2015.)


References


Questions

Hepatitis C Infection Treatment Revolution

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