CHRONIC HEPATITIS C: AN IMPROVED TREATMENT

JACQUELINE KOSTICK, PHARM.D.
Chronic Hepatitis C: An Improved Treatment

Activity Description
Hepatitis C virus (HCV) is a viral infection that injures the liver. It affects more than 170 million people worldwide. It is most frequently acquired from unsafe needle injections, unsterile medical equipment, or unscreened blood products. Among the six HCV genotypes, the most common in the U.S. is genotype 1, which is found in 60-70% of the HCV population. For years, a combination of interferon and ribavirin was the standard chronic HCV genotype 1 treatment; however, this regimen was ineffective for many people and associated with serious adverse effects. Recently, the U.S. Food and Drug Administration (FDA) approved several HCV oral treatments with the potential to change HCV treatment history.

Target Audience
The target audience for this activity is pharmacists and pharmacy technicians in hospital, community, and retail pharmacy settings.

Learning Objectives
After completing this activity, the pharmacist will be able to:
- Explain history, frequency, and diagnosis of chronic hepatitis C virus (HCV).
- Discuss HCV transmission and signs/symptoms.
- Outline and describe medications used to treat HCV (e.g., mechanisms of action, duration of treatment, and potential side effects).

After completing this activity, the pharmacy technicians will be able to:
- Explain history, frequency, and diagnosis of chronic hepatitis C virus (HCV).
- Discuss HCV transmission and signs/symptoms.
- List medications used to treat chronic HCV.

Accreditation

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Jacqueline Kostick PharmD is a pharmacist and medical writer. As the owner of JK Medical Writing, she has written and researched pharmacy-related material (e.g., medical newsletters, drug monographs, medical website content) for organizations including Medscape, the American Society of Health-System Pharmacists (ASHP), CVS/Caremark, and United HealthCare.

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Chronic Hepatitis C Virus (HCV): An Improved Treatment

Jacqueline Kostick, PharmD

Objectives

• Explain the history, frequency, and diagnosis of chronic hepatitis C virus (HCV).
• Identify the mode of HCV transmission and the associated signs/symptoms.
• Compare and discuss the recently approved medications used to treat HCV.

Chronic Hepatitis C Virus (HCV): An Improved Treatment

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Pharmacotherapy 11-30-2022 01-31-2023
Pharmacy Technicians 01-31-2023

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CE Credit(s)
Can’t hear? Contact Support.

Learning Objectives

• Explain the history, frequency, and diagnosis of chronic hepatitis C virus (HCV).
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Hepatitis Virus Transmission

<table>
<thead>
<tr>
<th>Types of Hepatitis</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Ingest food or water contaminated with infected fecal matter or sexual contact with infected person</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Contact with infected blood or body fluid (e.g., sexual contact, sharing needles, mother to baby)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Contact with infected blood or body fluid (e.g., sexual contact, sharing needles, mother to baby)</td>
</tr>
<tr>
<td>Hepatitis D (rare in US)</td>
<td>Contact with infected blood</td>
</tr>
<tr>
<td>Hepatitis E (rare in US)</td>
<td>Ingest food or water contaminated with infected fecal matter</td>
</tr>
</tbody>
</table>

Center for Disease Control and Prevention (CDC). Available at: www.cdc.gov
**Hepatitis Vaccines**

Hepatitis C virus does **not** have a vaccine.

<table>
<thead>
<tr>
<th>Types of Hepatitis</th>
<th>Vaccines Available in the U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>YES</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>YES</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>NO</td>
</tr>
<tr>
<td>Hepatitis D</td>
<td>NO</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>NO</td>
</tr>
</tbody>
</table>

**HCV Pathophysiology**

- Spherical, enveloped, single-stranded RNA virus (first described in 1989)
- Belongs to Flavivirus genus
- HCV virus targets liver cells

**HCV Genotypes**

- **Genotype 1a**: Occurs in 50-60% of US patients
- **Genotype 1b**: Occurs in 15-20% of US patients
- **Genotype 1c**: Occurs in <1% of US patients
- **Genotype 2 (a, b, c)**: Occurs in 10-15% of US patients (most responsive to medication)
- **Genotype 3 (a, b)**: Occur in 4-6% of US patients
- **Genotypes 4-6**: Each occur in <5% of US patients

**Hepatitis C Virus (HCV): Acute vs. Chronic**

- **Acute HCV infection**: Short-term illness that occurs within 6 months of exposure; usually progresses to chronic HCV infection.
- **Chronic HCV infection**: Long-term illness that can lead to serious liver problems (e.g., cirrhosis, liver cancer).
HCV Statistics

- 170 million people worldwide are infected with HCV
- 3.2 million people in the U.S. are infected with HCV.
- 75-85% of people with acute HCV will develop chronic HCV; remaining 15-25% acute HCV cases are self-resolving.
- Among chronic HCV patients, 15-30% will develop cirrhosis over time.

Chronic HCV Symptoms

Silent epidemic: Most HCV patients are asymptomatic in early stages.
- Fever
- Loss of appetite
- Nausea/Vomiting
- Stomach pain
- Dark (tea-colored) urine
- Clay-colored stools
- Jaundice (yellow color in skin or eyes)

Hepatitis C History

- 1989: Hepatitis C virus discovered by scientists at CDC and industry - previously called non-A, non-B hepatitis (NANB) in the US.
- 1996: Hepatitis C infections decline by 80% from 1989
- 2007: Deaths from hepatitis C surpass HIV in US (rates of new HCV cases decline but deaths due to HCV surpass HIV for first time)

HCV Transmission

Hepatitis C virus is a contagious liver infection.
- Sharing needles, syringes, injection equipment
- Needle stick injuries in healthcare setting
- Babies born to a mother with HCV
- Sexual contact
- Sharing razors or toothbrushes infected with blood
- Not spread by food or water, nor by sharing utensils, breastfeeding, hugging, kissing, or coughing
Populations at Risk for HCV

- Past and present injection drug users
- Blood recipients (rare since blood screening began in US in 1992)
- Hemodialysis patients
- Body-piercing or tattoos with infected instruments
- Needle-stick injuries with infected HCV blood
- Babies born to HCV infected mothers

HCV Testing

- Born between 1945-1965 should be tested at least once for HCV (75% of infected adults)
- Current of former injection drug user
- Treated for a blood clot before 1987
- Received a blood transfusion or organ prior to July 1992
- Long-term hemodialysis patient
- Exposed to blood from a needle stick (e.g., healthcare workers)
- HIV patients

HCV Treatment Goals

- Achieve an undetectable HCV RNA (a virologic cure) level 12 weeks after finishing therapy — a sustained virologic response (SVR) (per 2015 HCV guidelines)

- Prevent chronic HCV progression to cirrhosis, liver cancer, and eliminate the need for a liver transplant (per 2015 HCV guidelines)
Evolution of Treatment

**Interferon (IFN):** First used for Non-A, Non-B (NANB) hepatitis (or hepatitis C) in 1986 as it was used to treat hepatitis B virus.

- **1990s:** Several injectable IFNs approved for HCV that were given three times week.
- **SVR rate:** <10% for genotype 1
- **SVR rate:** 30% for genotypes 2 and 3

**Interferon (IFN)**

- Activates human type 1 interferon receptor to stimulate host gene cells with antiviral functions.
- Causes unnecessary actions in the body (e.g., suppresses cell cycle progression, stimulates cytotoxic T-lymphocytes).
- Previously used IFNs for HCV:
  - IFN alfa-2a (Intron-A®)
  - IFN alfa-2b (Roferon-A®)

**Interferon and ribavirin combination**

- IFN alfa-2a (Intron-A®) + ribavirin = (Rebetron®) - 1998
- Ribavirin along with IFN had synergistic effects to stop HCV from spreading in the body.
- **SVR:** Genotype 1: ~30%
- **SVR:** Genotypes 2 and 3: ~60%

**PEG-IFN**

- Adding a PEG molecule to IFN improves absorption and allows for weekly dosing.
- PEG-IFN alfa-2b (PEG-Intron®)
- PEG-IFN alfa-2a (Pegasys®)
PEG-IFN + Ribavirin

- **PEG-IFN alfa-2a (Pegasys®) + Ribavirin (Copegus®)** – Approved in 2002

- **Genotype 1 patients**: 48 weeks of therapy- **SVR rate: 44-51%**

- **Genotypes 2-3**: 24 weeks of therapy- **SVR rate: ~70%**

PEG-IFN + Ribavirin: Adverse Effects

- Blood complications: Neutropenia, thrombocytopenia, anemia
- Memory and confusion issues
- Visual disturbances
- Thyroid issues
- Hair loss
- Birth defects
- Gout

Medication for HCV Thrombocytopenia

Eltrombopag (Promacta®): Treatment of thrombocytopenia in HCV patients to help with IFN therapy.

- Stimulates bone marrow platelet production during IFN therapy
- Initially, 25 mg PO QD, may increase q 2 weeks PRN to achieve target platelet
- Do not exceed 100 mg/day

Stop Viral Replication

HCV is a RNA virus that forms a complex with non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, NS5B) when ready to replicate.
HCV NS3/4A Protease Inhibitors

First-generation
- Boceprevir (Victrelis®): Approved in 2011
- Telaprevir (Incivek®): Approved in 2011; discontinued in Nov 2014

Second-generation
- Simeprevir (Olysio®): Approved in Nov 2013

HCV Protease Inhibitor: Simeprevir (Olysio®)

- Inhibits HCV NS3/4A protease needed for proteolytic cleavage (blocks HCV viral replication)
- Used for HCV genotype 1 infection (in combination with other agents)
- Photosensitivity reaction: Limit sun exposure, use protective sun exposure measures

Simeprevir (Olysio®): Dosing

- 150 mg PO QD with PEG-IFN alfa (Pegasys®) and ribavirin (Copegus, Rebetol®)
  SVR: ~80%
- 150 mg PO QD in combination with sofosbuvir (Sovaldi®)
  SVR: ~90%

Sofosbuvir (Sovaldi®)

- Sofosbuvir slips into HCV RNA through NS5B polymerase to stop viral replication.
- Used for HCV genotypes 1, 2, 3, and 4 (in combination therapy).
Sofosbuvir (Sovaldi®)
SVR rate: 90% in HCV patients after 12 weeks of daily therapy.

• **Genotypes 1 or 4:** 400 mg PO QD for 24 weeks with PEG-alfa and ribavirin

• **Genotype 2:** 400 mg PO QD + ribavirin for 12 weeks

• **Genotype 3:** 400 mg PO QD + ribavirin for 24 weeks

Sofosbuvir and PEG-IFNα/RBV:
Dose Adjustment

• Sofosbuvir (Sovaldi®): Do not adjust dose

• PEG-IFN alfa (genotypes 1 and 4): Reduce or discontinue PEG-IFN alfa and/or ribavirin if serious side effects occur (e.g., anemia)

HCV Polymerase Inhibitor:
Ledipasvir

• HCV NS5A inhibitor that also stops the HCV virus life cycle by blocking a key step in replication.

• Not used alone; used in combination with sofosbuvir as Harvoni® (approved in Oct 2014)

Ledipasvir/Sofosbuvir (Harvoni®)

• When ledipasvir and sofosbuvir are given together, the two different anti-viral mechanisms of action have a synergistic effect.

• **SVR: 94-99%** in HCV genotype 1 patients (after 12-24 weeks of therapy)
Harvoni®

- Approved in 2014 for HCV genotype 1
- 1 fixed-combination tablet (90 mg/400 mg) PO QD – with or without food
- Duration of therapy: 8-24 weeks (depends on if patient has cirrhosis and is treatment-naïve)
- Adverse effects: Fatigue, headache

Harvoni®: Interactions

- Cardiovascular: amiodarone (Pacerone), digoxin (Lanoxin®)
- Seizure medications: carbamazepine (Tegecro®), phenytoin (Dilantin®), phenobarbital, oxcarbazepine (Trileptal®)
- HIV: efavirenz (Sustiva®), emtricitabine (Emtriva®), and tenofovir (Viread®) given alone or in combination regimens
- Tuberculosis: rifabutin (Mycobutin®), rifampin (Rifadin®)
- Depression: St. John's wort
- Cholesterol: rosvustatin (Crestor®)
- HCV: simeprevir (Olysio®)
- Antacids (e.g., Maalox, Mylanta, Tums): Take 4 hours before or 4 hours after Harvoni

Viekira Pak®

- Patients with chronic HCV genotype 1 infection-approved in Dec 2014
- SVR: 91 to 100% (PI states 97% SVR)
- Contains three new drugs—ombitasvir, paritaprevir and dasabuvir—that work together to inhibit HCV growth.
- Also contains ritonavir to increase blood levels of paritaprevir.
- Can be used with or without ribavirin

Viekira Pak®

- Schedule: Take 2 tablets in AM with food (ombitasvir, paritaprevir, ritonavir) and 1 dasabuvir tablet in AM and PM with food.
- Side effects: Itching, feeling weak, nausea, or trouble sleeping.
- Drug Interactions: Stop estrogen-based medications prior to treatment; switch to other birth control during therapy and continue 2 weeks after therapy.
- Warning: Do not use in patients with decompensated (advanced) cirrhosis.
### Viekira Pak +/- RBV: Dosing Regimen

<table>
<thead>
<tr>
<th>HCV</th>
<th>Treatment</th>
<th>Duration (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a, without cirrhosis</td>
<td>Viekira Pak + Ribavirin (RBV)</td>
<td>12</td>
</tr>
<tr>
<td>Genotype 1b, without cirrhosis</td>
<td>Viekira Pak</td>
<td>12</td>
</tr>
<tr>
<td>Genotype 1a, with cirrhosis</td>
<td>Viekira Pak + RBV</td>
<td>24**</td>
</tr>
<tr>
<td>Genotype 1b, with cirrhosis</td>
<td>Viekira Pak + RBV</td>
<td>12</td>
</tr>
</tbody>
</table>

### Cost of New HCV Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>12-weeks of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/sofosbuvir (Harvoni®)</td>
<td>$113,400 ($1350 per tablet)</td>
</tr>
<tr>
<td>Sofosbuvir (Sovaldi®) + Peg IFN-α-2 (Pegasys®) and ribavirin (generic)</td>
<td>$84,000 (Sovaldi®) + $9,250 (PEG IFN-α-2) + $700 generic ribavirin = $93,950</td>
</tr>
<tr>
<td>Sofosbuvir (Sovaldi®) + simeprevir (Olysio®) +/- ribavirin (generic)</td>
<td>$84,000 (Sovaldi®) + $66,300 (Olysio®) + $700 generic ribavirin = $151,000</td>
</tr>
<tr>
<td>Ambisasev- poritaprevir- ritonavir and dasabuvir (Viekira Pak®) +/- ribavirin (generic)</td>
<td><strong>$83,319</strong> OR - if token + generic ribavirin $700 = <strong>$84,019</strong></td>
</tr>
</tbody>
</table>

### New HCV Medications
- **Simeprevir (Olysio®)**: Nov 2013
- **Sofosbuvir (Sovaldi®)**: Dec 2013
- **Ledipasvir/sofosbuvir (Harvoni®)**: Oct 2014
- **Viekira Pak®**: Dec 2014
- **Daclatasvir (Daklinza®)**: July 2015

### Daclatasvir (Daklinza®)
- Approved in July 2015 for **HCV genotype type 3 patients**
- Oral tablet (60 mg) given once daily (with or without food)
- Must be given with sofosbuvir (Sovaldi) 400 mg PO QD
- Contraindication: Do not give along with CYP3A Inducers
  - Phenytoin
  - Carbamazepine
  - Rifampin
  - St. John’s Wort
Ombitasvir, Paritaprevir and Ritonavir (Technivie®)

- Approved in July 2015 for genotype 4 HCV patients without scarring and cirrhosis--without the need for IFN
- All-oral, fixed-dose combination of 2 tablets given once daily with a meal
- Paritaprevir/ritonavir (150/100 mg) with ombitasvir (25 mg) + weight-based ribavirin (1000 mg or 1200 mg in divided doses, twice daily) taken with food- if patient can tolerate RBV

Ombitasvir, Paritaprevir and Ritonavir (Technivie®)

- PEARL-I study: 100% SVR12 in patients who received Technivie® and RBV for 12 weeks

- Drug Interactions: Stop estrogen-based medications prior to treatment; switch to other birth control during therapy and continue 2 weeks after therapy.
- Contraindications: CYP3A inducers (e.g., phenytoin, carbamazepine, rifampin, St. John’s Wort)

Breakthrough HCV Treatment

- IFN-free regimens
- Potential for all-oral, once-daily regimens
- Minimal side effects
- Duration of therapy: 8-24 weeks (instead of up to 48 weeks)
- Effective treatments for challenging to treat genotype 1 HCV patients

HCV Practice Guidelines: Constantly Updating

- AASLD/IDSA/IAS Practice Guidelines for the Diagnosis, Management, and Treatment of Hepatitis C
- (Web-based guidelines)
  Available at: http://www.hcvguidelines.org/fullreport
HCV Guidelines Update

HCV genotype 1a or 1b infection:

1. Ledipasvir/sofosbuvir for 12-24 weeks (Grade 1A) (depending on cirrhosis)
2. Viekira Pak + RBV for 12 weeks (no cirrhosis) (Grade 1A) 24 weeks (with cirrhosis) Grade 1B
3. Sofosbuvir + simeprevir for 12-24 weeks (Grade 2a-B)

“Antiviral treatment is recommended for all patients with chronic HCV infection, except those with limited life expectancy due to non-hepatic causes.” (Grade I-A)

HCV Guidelines (as of June 2015)

Tips for HCV Patients

- Go to all medical appointments
- Importance of medication adherence
- Avoid alcohol
- Talk to doctor/pharmacist about their medications that are liver-metabolized
- Check with doctor before hepatitis A and B vaccines (if liver damaged by HCV)
- Do not donate blood, organs, or semen

Thank you! Questions?