Sofosbuvir: Game Changer for the Treatment of Hepatitis C

Leslie Dixon, Pharm.D.
Managed Care Drug Policy Resident
Scott & White Health Plan
Temple, TX

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Learning Objectives

1. Describe Hepatitis C patient demographics
2. Discuss the evidence for sofosbuvir in Hepatitis C genotype 1 patients
3. State sofosbuvir’s place in therapy according to the AASLD
4. List several ways in which sofosbuvir is a game changer for patients, insurers, and dispensing pharmacists
Hepatitis C virus (HCV): disease course and demographic trends

- Prevalence:
  - 170-200 million worldwide
  - 3-4 million people in U.S.
    - 75% born between 1945-1965 ("baby boomers")
      - majority unaware they are infected
    - 45,000 inmates in Texas

- RNA virus with a high mutation rate
  - Rapid evolution evades the immune response
  - 85% exposed chronically infected
  - Lifelong immunity impossible.
- If a person is cured of hepatitis C, they can become reinfected again to the same strain or subtype

Hepatitis C virus: 6 genotypes
- Genotype 1: 70% of all cases in the United States
  - Two subtypes: 1a and 1b
  - Historically, the most difficult to treat
- Genotypes 2 and 3
- Genotype 4, 5 and 6 are rare in U.S.

Natural History of Hepatitis C Infection

- Age is the most significant factor associated with progression
  - Acquisition at age 50: progress to cirrhosis in 10 years
  - Acquisition at age 20: progress to cirrhosis in 30-40 years
- Other factors associated with rapid progression male sex, HIV or HBV co-infection, and alcohol use are also associated with faster progression
<table>
<thead>
<tr>
<th>HCV Medications</th>
<th>Approval Year</th>
<th>Mechanism of Action</th>
<th>SVR Rate for Genotype 1 (upper limit)</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon α-2 + Ribavirin (&quot;PEG/RBV&quot;)</td>
<td>2001</td>
<td>• Interferons ↑ macrophage phagocytosis and lymphocyte cytotoxicity</td>
<td>50%</td>
<td>Anemia (may require transfusion)</td>
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<td>• Ribavirin inhibits replication of RNA and DNA viruses</td>
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<td>Flu-like sx</td>
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<td>Anxiety, depression, memory loss, acute psychoses, suicidal ideation</td>
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<td>Hearing loss, seizures, vision loss, coma</td>
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<td>Renal, cardiac, pulmonary failure</td>
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<td>Autoimmune disease</td>
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<td>MI, angina, stroke</td>
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<td>Hair loss, rash, photosensitivity</td>
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<td>Injection site pain</td>
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<tr>
<td>Boceprevir and Telaprevir</td>
<td>2011</td>
<td>Prevent viral proteases from cleaving nonstructural proteins into replication complex</td>
<td>70%</td>
<td>↑ PEG/RBV side effects</td>
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<td></td>
<td></td>
<td></td>
<td>Dysgesia</td>
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<td></td>
<td>Severe rash</td>
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<td></td>
<td>Neutropenia</td>
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<td>Photosensitivity</td>
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<tr>
<td>Sofosbuvir</td>
<td>2013</td>
<td>Decoy substrate for HCV RNA polymerase (NS5B portion); chain terminator</td>
<td>90%</td>
<td>Fatigue</td>
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<td></td>
<td></td>
<td>Headache</td>
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<td>Nausea</td>
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</tbody>
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**NEUTRINO trial: Sofosbuvir for HCV Genotype 1**

- **Sovaldi (sofosbuvir)**
  - In phase 1-2 trials:
    - Well tolerated with few side effects
    - 12-week treatment regimen
    - High cure rate: ATOMIC phase II trial SVR12 90% (n = 332)

- Key exclusion criteria
  - HIV
  - hepatitis B
  - psychiatric disease
  - solid organ transplant
  - decompensated liver disease
  - cancer
  - alcohol > 3 glasses/day

- 327 treatment naïve subjects
- Single arm, open-label trial with historical control
  - Standard-of-care protease inhibitor as a comparator arm was impractical because:
    - Sovaldi trials could enroll any genotype
    - Sovaldi treatment duration is 3 months vs. 6-12 months for a protease inhibitor
    - SVR checks during treatment are unnecessary because 99% have undetectable virus by week 4
    - FDA did not want to expose patients to a less effective comparator arm

**SVR12 = 90%**

<table>
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<tr>
<th>Difficult to treat characteristics</th>
<th>% Cohort (n = 327)</th>
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<tbody>
<tr>
<td>Cirrhosis</td>
<td>80%</td>
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<tr>
<td>IL28B Non-CC</td>
<td>87%</td>
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<tr>
<td>Black race</td>
<td>87%</td>
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<tr>
<td>Hispanic race</td>
<td>91%</td>
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</tbody>
</table>
NEUTRINO trial: Sofosbuvir for HCV Genotype 1

- Genotype 1a: 92% [87%, 95%]
- Genotype 1b: 82% [70%, 90%]

The only difference in the RNA polymerase between these two subtypes is amino acid C316N
- If C316N is substituted with a larger side chain, Sovaldi cannot bind the active site

C316N
- highly conserved in genotype 1a (99.89%)
- less conserved in genotype 1b (81.83%)

The FDA concluded the difference in efficacy is due to this polymorphism
There is no commercially-available test to detect the presence of the 1b polymorphism

Genotype 1 patients who had failed prior therapies have been waiting for a drug like Sofosbuvir, but NEUTRINO only studied treatment naïve patients

There are many hepatitis C patients who are intolerant to interferons

They have never had a treatment option because all regimens include interferon
PHOTON-1 trial: Sofosbuvir for HCV Genotype 1

**ADULTS CO-INFECTED WITH HCV and HIV-1**

<table>
<thead>
<tr>
<th>STUDY ARMS*</th>
<th>N=223</th>
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<tbody>
<tr>
<td>SofOS + TDF</td>
<td>GT 1  24 WEEKS</td>
</tr>
<tr>
<td>SofOS + TDF</td>
<td>GT 2  12 WEEKS</td>
</tr>
<tr>
<td>SofOS + TDF</td>
<td>GT 3  24 WEEKS</td>
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</tbody>
</table>

HIV + HCV co-infected
Sofvaldi + Ribavirin x 24 weeks
SVR12 = 76.3% (n = 114)

**Genotype 1: HIV-HCV Co-Infected**

<table>
<thead>
<tr>
<th>HCV Mono-infected and HCV/HIV-1 Co-infected</th>
<th>Treatment</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Genotype 1 or 4</td>
<td>SOVALDI + peg-</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>interferon alfa +</td>
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<tr>
<td></td>
<td>ribavirin</td>
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</tbody>
</table>

Supporting data the FDA used to evaluate this regimen could not be located

**Breakthrough Status Approval**

**Sofosbuvir: New Standard of Care**

Sofosbuvir is recommended *first line* for all genotypes
Boceprevir and telaprevir protease inhibitors are not recommended

**Sofosbuvir: Game Changer for Patients**

- Most effective treatment to date
  - NEUTRINO TRIAL: 90% CURE RATE
- Option of interferon-free regimen
  - PHOTON-1 TRIAL FOR GENOTYPE 1: 73.6% CURE RATE
- Short treatment course
  - Duration 3 months – 6 months
- Better tolerated
  - Fatigue, headache, and nausea
Sofosbuvir: Game Changer for Insurers

Screening of Baby Boomers

- 2-3 million baby boomers have Hepatitis C
- Most do not know they are infected
  - CDC: one-time screening for all baby boomers

The most expensive outpatient unit dose ever brought to market

\[
\text{Sovaldi + PEG/RBV} \times 12 \text{ weeks} = \$100,000
\]

\[
\text{Sovaldi + RBV} \times 24 \text{ weeks} = \$175,000
\]

"What they have done with this particular drug will break the country," said Express Scripts CMO Miller

Gilead has negotiated a price break with Egypt. A 12-week course of sofosbuvir will cost $900

Texas prisons

45,000 inmates with Hepatitis C
Sovaldi 12-week regimen $100,000

Cost of cure: 4.5 billion dollars

Actuarial costs not priced in
- An insurance plan cannot readily react to significant shifts in outlay

Is cost-sharing feasible?
- Maximum out-of-pocket is usually $10,000 per year or less
  - Insurers pay the rest

Sofosbuvir: Game Changer for Dispensing Pharmacists

Each Sovaldi bottle costs approximately $28,000
- Should Sovaldi be available by mail order?
- Retail pharmacies will not dispense due to high carrying costs

Potential roles for the pharmacist
- House calls
- Refill reminder service
  - If not refilled, notify prescriber?
- Low health literacy handouts

Sovaldi must be dispensed in the original container
- What if the patient loses a few tablets?

Questions?

Contact information: lesliedixon@mac.com
References


Dugum M. Cleveland Clinic Journal of Medicine 2014; 81(3):159-172.


