Management of Hepatitis C Infection: Promises and Challenges Ahead

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Overview

The current landscape of hepatitis C in the United States

Newly approved directly acting antiviral agents (DAAs) in different patient populations

Future therapeutic options beyond 2014

The Washington DC HCV experience (DCPFAP)
Hepatitis C: Epidemiology

- Estimated 170 million persons with HCV infection worldwide
- 3-4 million newly infected each year worldwide

Prevalence of infection:
- > 10%
- 2.5–10%
- 1–2.5%

Source: ©WHO, 2008. All rights reserved.
Deaths From Hepatitis C Have Surpassed Deaths From HIV Infection

Age-adjusted Mortality Rates of HIV and Hepatitis C: United States, 1999-2010

Projected Cases of Hepatocellular Carcinoma and Decompensated Cirrhosis Due to HCV

- Decompensated cirrhosis
  - Peak incidence: 145,000 cases/year in 2020

- Hepatocellular cancer
  - Peak incidence: 14,000 cases/year in 2019

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Causes of Chronic Liver Disease Among Alaskan Indian Population

HCV Is Largely Underdiagnosed In The U.S

Number of infected persons vs number aware of their infection (diagnosed)

HIV: 21% Undiagnosed, 89% Diagnosed
HBV: 65% Undiagnosed, 35% Diagnosed
HCV: 75% Undiagnosed, 25% Diagnosed

Institute of medicine: Hepatitis and Liver Cancer: A national strategy for prevention and control 2010
CDC HCV Screening Recommendations

CDC now recommends

• Age based testing: All adults born during 1945 – 1965 should have a one-time antibody testing without prior ascertainment of risk
• Referral to care
• Alcohol screening and intervention

If tested and treated,
-> 120,000 deaths averted
- > $2.5 billion medical costs averted

MMWR Aug 17, 2012; Rein D et al, Ann Int med 2012: 156
## Primary concerns pertaining to HCV screening

<table>
<thead>
<tr>
<th>Concern</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of treatment for hepatitis C</td>
<td>54.2%</td>
</tr>
<tr>
<td>Referral facilities for HCV patients</td>
<td>45.8%</td>
</tr>
<tr>
<td>Treatment options for HCV patients</td>
<td>41.7%</td>
</tr>
<tr>
<td>Cost of increasing HCV screening</td>
<td>39.6%</td>
</tr>
<tr>
<td>Clinical training on HCV</td>
<td>37.5%</td>
</tr>
<tr>
<td>Implementing HCV screening</td>
<td>31.3%</td>
</tr>
<tr>
<td>Rationale of CDC recommendations for age-based screening</td>
<td>14.6%</td>
</tr>
</tbody>
</table>

Annual Hospitalization Rates as a Result of Hepatitis

Byrd KK et al. Public Health Reports, 2011, 126: 816-825
Annual Hospitalizations due to Hepatitis C by Age Group

Annual Hospitalizations due to Hepatitis C by Region

Patients with Advanced Liver Disease Progress Rapidly

HCV Infection in the U.S: Estimated Rates of Detection, Referral to Care, and Treatment

- Total U.S. Population with chronic HCV infection: 3,500,000
- HCV Detected: 50%
- Referred to Care: 32-38%
- HCV RNA test: 20-23%
- Underwent liver biopsy: 12-18%
- Treated: 7-11%
- Successfully Treated: 5-6%

SVR and Reduced Risk of All-Cause Mortality - U.S. Veterans Study

21,839 treated patients in VA Clinical Case registry; 16,864 with f/u
- high rates of co-morbidities (DM, HTN, ETOH, CAD)
SVR:  G1: 35%, G2: 72%, G3 62%

HCV Genotype 1

$P \text{ (log-rank) } < 0.0001$

Treatment of HCV
Advances in Chronic Hepatitis C Treatment

Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, 2011.
The Promise of Interferon-free DAA Therapy

Specific drugs
- Boceprevir
- Telaprevir
- Faldaprevir
- Asunaprevir
- Daclatasvir
- Simeprevir
- Sofosbuvir
- ABT-333
- ABT-450/r
- Ledipasvir
- ABT-267

Non-specific drugs
- PEG-IFNα
- Ribavirin
- NS3/4A PI
- Nucleoside NS5B inhibitor
- NS5A inhibitor
- Non-Nuc NS5B inhibitor
- Non-specific agent

HCV Life Cycle and DAA Targets

Telaprevir
Boceprevir

Simeprevir

NS3/4 protease inhibitors

ER lumen
Translation and polyprotein processing

Cyclophilin inhibitors
Transport and release

Virion assembly

LD
NS5B polymerase inhibitors

RNA replication

NS5A inhibitors*
*Role in HCV lifecycle not well defined

Hadigan C and Kottilil S. JAMA 2011
Primary concerns pertaining to HCV treatment

<table>
<thead>
<tr>
<th>Reason</th>
<th>2003 (%)</th>
<th>2007 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to attend scheduled clinic appointments</td>
<td>32 (36%)</td>
<td>24 (16%)</td>
</tr>
<tr>
<td>Alcohol or drug abuse within 6 months</td>
<td>16 (17%)</td>
<td>29 (22%)</td>
</tr>
<tr>
<td>Patient decision to defer treatment</td>
<td>16 (17%)</td>
<td>36 (25%)</td>
</tr>
<tr>
<td>Liver biopsy without fibrosis or normal ALT</td>
<td>8 (8%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Uncontrolled psychiatric condition</td>
<td>7 (7%)(^a)</td>
<td>9 (6%)(^b)</td>
</tr>
<tr>
<td>Concurrent medical condition precluding treatment</td>
<td>6 (6%)(^c)</td>
<td>12 (8%)(^d)</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>3 (3%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>2 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Considering or planning treatment</td>
<td>0</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>132</td>
</tr>
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</table>

Livingston SE et al. *Int J Circumpolar Health* 2012, 71: 18445
Future HCV Treatment Strategies

**Phase III Treatment-naive**

- **Peg-IFNa-containing regimens**
  - 2nd Gen. PI Triple
    - Faldaprevir, Simeprevir
  - NUC Triple
    - Sofosbuvir HCV type 1 and 4-6

**Next wave of triple/quadruple regimens**

- Asunaprevir (PI)
- MK5172 (PI)
- MK7009 (PI)
- Daclatasvir (NS5A)
- GS8558 (NS5A)
- Daclatasvir + Asunaprevir
- GS5885 + GS9451

**Phase III IFN-free regimens**

- NUC + RBV
  - Sofosbuvir HCV type 2 and 3

**Next wave of all-oral regimens**

- ABT-450/r (PI/r)+ABT-267 (NS5A)+ABT-333 (NNUC)+RBV
- Faldaprevir + BI 207127 + RBV
- Daclatasvir (NS5A) + Sofosbuvir (NUC) ± RBV
- GS5885 (NS5A) + Sofosbuvir (NUC) ± RBV
- GS9669 (Non-NUC) + Sofosbuvir (NUC) RBV
- Asunaprevir (PI) + Daclatasvir (NS5A) + BMS791325

PI = Protease Inhibitor, NUC = nucleosidic polymerase (NS5B) inhibitor, NS5A = NS5A Inhibitor, PI/r ritonavir boosted PI, RBV = Ribavirin
Summary

- New standard of care for HCV GT-1
  - Simeprevir / PegIFN/RBV : GT-1
  - Sofosbuvir/RBV: GT-2, 3, ?1 (+ PegIFN/RBV: GT-1)
- Future therapies likely IFN free +/- RBV
- Important advances for treatment in prior difficult to treat populations (cirrhosis, HIV/HCV, transplant)
- Identification, retention in care and delivery of new DAA therapies in the U.S and globally is the next step.
- Pathway going forward either:
  - Simple, once daily, 1-2 pills, pangenotypic regimens
  - OR
  - Individualized considering genotype, comorbidities, DDI, pre-existing mutations, fibrosis etc
NIH - District Of Columbia Partnership For AIDS Progress (DCPFAP)

Federal – local partnership
Washington DC: HCV prevalence ~1.8%
– Over 13,000 chronic HCV cases
Urban model for HIV and hepatitis management and translational research

HCV Prevalence

Location of NIH-supported Clinics

NIH Clinical Center
Key Points

- First Interferon-free regimen in the USA
- First Interferon-free regimen for difficult to treat patient population
- Established biological correlates for relapse for sofosbuvir and ribavirin
- First interferon and ribavirin free regimen for HIV/HCV coinfected subjects
- First Interferon and ribavirin free regimen for HCV genotype 4 patients
- First study to retreat previous relapsers of sofosbuvir containing regimen
- First study to demonstrate you can shorten duration of therapy by adding DAAs
Strategy for HCV Cure

Emerging HCV Therapy

- High cure rate
- All oral therapy
- Low pill burden
- Shorter course
- Fewer side effects

- Durability of response
- Reinfection
- Resistance
- Screening
- Linkage to care
- Economics
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