Hepatitis C: Eradication of a Disease?

Gordon Dow, MD
Oct 16th, 2015
Disclosures:

In the past two years I have participated in research\(^1\) or received consultation/speaking fees\(^2\) from:

- Astellas\(^2\)
- Abbvie\(^1,\,2\)
- Amgen\(^2\)
- Gilead\(^2\)
- Merck\(^1,\,2\)
- Paladin\(^2\)
Objectives

By the end of this presentation participants should be able to:

(1) Describe the morbidity, mortality and cost of untreated HCV

(2) Review the clinical, histological and virological evidence that hepatitis C is curable

(3) Summarize the dramatic improvement in HCV cure with recently approved direct acting anti-viral agents (DAA’s)
Natural History of HCV Infection

HCV Exposure → Acute Infection

- Most Asymptomatic
  - 20-25% of patients

Stages:

- Chronic Infection
  - 50-85% of patients
  - 1-4%/year

- Cirrhosis
  - 20-25% of patients

- Liver Failure
  - 1-4%/year

- HCC

- Liver Transplant or Death

Viral eradication stops progression of liver disease and improves clinical outcomes.
Hepatitis C, of all infectious diseases, is responsible for highest increase in premature mortality in Canada
Hepatitis C Medical Burden:

HCV increases all cause mortality.

Hepatitis C is Curable:

• SVR 12 predicts persistent absence of virus
• Attainment of SVR associated with:
  – regression of liver disease
  – reduced all-cause mortality
  – reduced risk of liver failure and need for transplantation
  – reduced risk of HCC
  – Improved cognitive function and quality of life
SVR 12 = Hepatitis C Cure

Concordance of SVR Rates Using Sofosbuvir –Containing Regimens
(78% of relapses occurred within the first 4 weeks, 98% by 12 weeks)

Long-Term Follow-up of HCV Treatment Success Consistent With Cure

- 54 patients with median duration of HCV infection x 18 years
- Successfully treated with interferon-based regimen with 10 year follow-up post-SVR
  - clinical, biochemical and histological regression/normalization
  - HCV specific antibody titres ↓ over time
  - HCV specific T-cell responses ↓ over time
  - HCV RNA(-) by ultracentrifugation/RT-PCR in plasma (54/54), liver biopsy (40/40) and PBMC’s (51/54)

Attainment of SVR associated with:

Reduced liver related and all cause mortality.

Reduced HCC and liver failure.
HCC Incidence over time in F4 patients according to SVR status.

Median Follow up 10 years
Curing Hepatitis C is About More Than The Liver

- Cures extrahepatic manifestations related to chronic HCV infection
  - Mixed cryoglobulinemia and leukocytoclastic vasculitis
  - B-cell non-H Hodgkin lymphoma
  - Porphyria cutanea tarda
  - Reduced steatosis/insulin resistance

Cacoub P et al Dig Liver Dis 2014;46:S165-173
Lim T et al Hepat Med 2014;6:113-18
Treatment Evolution:

- Oral Combo therapy
- Peg IFN-RIBA-PI
- Peg IFN-RIBA
- IFN/RIBA
- IFN Monotherapy
The HCV DAA Explosion:

- 9.6 KB RNA Genome
- 5' to 3'
- C (Core) E1 E2 p7 NS2 NS3 NS4A NS4B NS5A NS5B
- Core, Envelope, Protease, Serine Protease and Cofactor, RNA binding, RDRP
- NS3/4A Protease Inhibitors
- NS5A Inhibitors
- Nuc and Non Nuc NS5B Polymerase Inhibitors
Ledipasvir/Sofosbuvir:

- **Ledipasvir/Sofosbuvir STR**
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet
  - No food effect
  - >2000 patients treated
ION Phase 3 Program (ION-1, ION-2, ION-3) Efficacy Summary

- 97% (1886/1952) overall SVR rate
- 3% (66/1952) did not achieve SVR
  - 1.4% (28) LTFU
  - 0.1% (2) virologic breakthrough (both due to non-adherence)
  - 1.8% (36) relapsed. Patients may be rolled over to a retreatment study

HOLKIRA PAK Recommended Dosage

- The recommended oral dose of HOLKIRA PAK is two ombitasvir/ABT-450/ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) for 12 weeks.

- HOLKIRA™ PAK is used in combination with ribavirin in certain patient populations.

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Genotype 1b, without cirrhosis</td>
<td>HOLKIRA™ PAK</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a, without cirrhosis</td>
<td>HOLKIRA™ PAK + ribavirin*</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotypes 1a and 1b, with cirrhosis</td>
<td>HOLKIRA™ PAK + ribavirin</td>
<td>12 weeks†</td>
</tr>
</tbody>
</table>

* HOLKIRA™ PAK without ribavirin can be considered as a therapeutic option for treatment-naïve patients with genotype 1a infection without cirrhosis who are intolerant of or ineligible for ribavirin (see CLINICAL TRIALS). Treatment decision should be guided by an assessment of the potential benefits and risks for the individual patient.

† 24 weeks of HOLKIRA™ PAK + ribavirin is recommended for patients with genotype 1a-infection with cirrhosis who have had a previous null response to pegylated interferon (pegIFN) and ribavirin (see CLINICAL TRIALS).

Note: HOLKIRA™ PAK with ribavirin is recommended in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
Phase 3 Program Clinical Data: Efficacy (SVR12)

SVR12 (%)

- **SAPPHIRE-I**: 96, 95, 98
- **SAPPHIRE-II**: 96, 96, 97
- **PEARL-III**: 99.5, 99
- **PEARL-II**: 97, 100
- **PEARL-IV**: 97, 90
- **TURQUOISE-II**: 92, 96

**Subtype**
- All G1a G1b
- RBV No RBV

**Cirrhosis**
- x

**Tx Hx**
- Naïve
- Exp

**12w 24w**
- ✓ ✓

**GT1a/b GT1a GT1b GT1a GT1a/b**

Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic HCV Genotype 1, 4, or 6 Infection
A Randomized Trial
Stefan Zeuzem, MD; Reem Ghalib, MD; K. Rajender Reddy, MD; Paul J. Pockros, MD; Ziv Ben Ari, MD; Yue Zhao, PhD; Deborah D. Brown, BS; Shuyan Wan, PhD; Mark J. DiNubile, MD; Bach-Yen Nguyen, MD; Michael N. Robertson, MD; Janice Wahl, MD; Eliav Barr, MD; and Joan R. Butters, MD
ASTRAL Phase 3 Program (ASTRAL-1, ASTRAL-2, ASTRAL-3, ASTRAL-4)

Efficacy Summary (ITT Analysis)

- **In ASTRAL 1-3, SOF/VEL for 12 weeks had similar AEs compared with PBO in ASTRAL-1**
  - 2 subjects (0.2%) discontinued due to AEs
- **In ASTRAL-4, treatment-emergent SAEs occurred in 18% of subjects**
  - Most common AEs were fatigue, nausea and headache
  - Anemia was reported in 31% of subjects in the SOF/VEL+RBV arm and 4% and 3% treated with SOF/VEL for 12 or 24 weeks, respectively

Screening and Treatment are Cost-Effective in Canada

<table>
<thead>
<tr>
<th>Age Group Screened</th>
<th>Strategy</th>
<th>ICER ($)</th>
<th>HCV Deaths Prevented (per 10,000 screened)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-64</td>
<td>Screen and treat with PegIFN/RBV</td>
<td>38,117</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Screen and treat with DAA</td>
<td>34,783</td>
<td>18</td>
</tr>
<tr>
<td>45-64</td>
<td>Screen and treat with PegIFN/RBV</td>
<td>34,359</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Screen and treat with DAA</td>
<td>35,562</td>
<td>21</td>
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</tbody>
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*Wong W et al. CMAJ, Jan 2015*
Summary

• Hepatitis C in Canada is associated with significant mortality, morbidity and cost
• Compelling clinical, biochemical, histological and virological evidence that SVR 12 = CURE
• Cure achievable in >95% of treated patients
• Global eradication impossible
• Thanks!

   - Dr. Dan Smyth
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   - Dr. Lisa Barrett
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   - Dr. Connie Hoare

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   - Dr. Morris Sherman
   - Dr. Lamont Sweet
   - Dr. John Gill
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   - Lisa Frachette

R.E.C.A.P.
Centre for Research, Education & Clinical Care of At-Risk Populations