Hepatitis: transitioning to highly effective therapies

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Disclosures:
In the past two years I have participated in research¹ or received consultation/speaking fees² from:
- Abbvie¹,²
- Gilead²
- Merck¹,²

Objectives
(1) To review the clinical and health economic impact of untreated HCV.
(2) To review the potential impact of increased treatment using novel HCV regimens.
(3) To discuss optimal models of care designed to evaluate the clinical, epidemiologic, and economic impact of HCV treatment.

Natural History of HCV Infection

HCV Exposure → Acute Infection → Chronic Infection → Cirrhosis → Liver Failure → HCC → Liver Transplant or Death

Most Asymptomatic
20-25% of patients
1-4%/year

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.

HCV related mortality now exceeds that of HIV

Ontario Agency for Health Promotion and Protection, 2010
Ly et al, Ann Intern Med 2012

[Image of natural history of HCV infection diagram]

[Image of graph showing HCV, hepatitis B, and HIV related mortality]
Hepatitis C Medical Burden:

*HCV increases all cause mortality.*


Attainment of SVR associated with:

- Reduced liver related and all cause mortality.
- Reduced HCC and liver failure.

Van der Meer, JAMA 2012

HCC Incidence over time in F4 patients according to SVR status.

*[Image showing incidence over time.*

Median Follow up 10 years

Vanamangalam EASL 2014 Abstract 0125

The coming Wave of Liver Disease

- Driven largely by chronically infected baby boomer population.
- HCV leading cause of hepatic adverse outcome including liver transplantation in North America.
- Curative well tolerated therapies will increase treatment demand and require global management plan with stratified access.

O’Leary et al, Gastroenterology, 2008; Myers et al, CJGH, 2014

2013-2030 Predictions

- **45%**↑ Liver cirrhosis
- **90%**↑ Liver related death
- **35%**↑ Decompensated cirrhosis
- **120%**↑ Hepatocellular carcinoma

Versus 2013, increase in compensated cirrhosis, decompensated cirrhosis, HCC and liver related deaths 89%, 80%, 205%, and 160%


- Using Canadian data and system dynamic framework for 36 age/sex cohorts, modeled disease progression and cost in Canada 1950-2035.
- Assumptions include:
  - 70% of infected population diagnosed.
  - 77% viremic.
  - Modeled IFN/RBV treatment using historical data and treatment dispensing in Canada.
  - Peak comp/decompensated cirrhosis in 2031 (36,210/3380 cases).
  - Peak HCC 2035 at 2220 cases.
  - Peak mortality 2034.
  - 32,460 deaths 2013-2035 from liver related causes.

Myers et al, Can J Gastroenterol Hepatol, 2014

Curative well tolerated therapies will increase treatment demand and require global management plan with stratified access.
Average annual all-cause healthcare costs are increased with HCV (US):

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Mean per person annual healthcare cost (2010 USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV uninfected</td>
<td>9979</td>
</tr>
<tr>
<td>HCV+, non-cirrhotic</td>
<td>17,277</td>
</tr>
<tr>
<td>HCV+, compensated cirrhotic</td>
<td>22,752</td>
</tr>
<tr>
<td>HCV+, ESLD</td>
<td>59,995</td>
</tr>
<tr>
<td>HCV+, HCC</td>
<td>112,537</td>
</tr>
<tr>
<td>HCV+, OLT</td>
<td>145,045</td>
</tr>
</tbody>
</table>

US Insurance claims data > 50,000 persons 2002-2010
Cost 247% higher with ESLD versus non cirrhotic independent of age or other comorbidities (>93% ambulatory, inpatient, and pharmacy).

Prevalence of HCV decreases while cost increases due to treatment of late complications.

Hepatitis C: Significant Burden of Disease

Hepatitis C is the main cause of liver transplantation. In 2012:
- 494 people received liver transplants
- 492 people remained on the transplant list
- 62 people died waiting for a transplant

Indirect cost: $2,575 M (2013 USD).
Total 3.1 Billion (1.4% GDP).

Indirect costs exceed direct medical costs

- Egypt:
  - Modelling of direct/indirect costs 2013.
  - Direct costs for each disease state from national government hospital.
  - Indirect costs by WHO DALY template.

  - YLD from chronic cirrhosis (F0-F3), compensated cirrhosis, HCC and EHM (DM, NHL).
  - YLL due to decompensated cirrhosis, HCC, and EHM.

Indirect cost savings: SVR12 improves PRO and QOL even with advanced Fibrosis

Treatment:

Treatment Evolution:

Sustained Virologic Response (SVR) in the IFN era

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment duration (weeks)</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>60</td>
</tr>
</tbody>
</table>

History:

- 2001: PEG-IFN and RBV therapy.
- Summer 2011: Health Canada approves BOC/TVR for G1 treatment (with PR).
- Nov 2013: Health Canada approves Simeprevir for G1 treatment (with PR).
- Dec 2013: Health Canada approval of Sofosbuvir (SOF):
  - With PR for GT1 and 4
  - With RBV alone for G2 and G3

= IFN FREE!!

SVR in GT1 with BOC and TVR

Real world experience and cost

- TVR: registration trials 64-75% SVR
- Real world experience: HCV TARGET³, 90 centers, > 2000 patients, overall SVR 54%, 90% with AE leading to treatment change, serious AE in >10%.
- Real world median cost of SVR in 147 patients 189,338 (2012 USD), with close to 10% of cost spent on AE management².
The HCV DAA Explosion:

- 9.6 KB RNA Genome
- Core
- Envelope
- Protease
- Serine Protease and Co-factor
- RNA binding, RdRp
- NS3/4A Protease Inhibitors
- NS5A Inhibitors
- Nuc and Non Nuc NS5B Polymerase Inhibitors

Phase 3 Program – Evaluation in Broad Range of GT1 Patient Populations, with and without RBV

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Regimen</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>M13-046 (SAPPHIRE-I)</td>
<td>GT1, non-cirrhotic, treatment-naive</td>
<td>3-DAA + RBV vs placebo for 12 weeks</td>
<td>631</td>
</tr>
<tr>
<td>M13-098 (SAPPHIRE-II)</td>
<td>GT1, non-cirrhotic, treatment-experienced</td>
<td>3-DAA + RBV vs placebo for 12 weeks</td>
<td>296</td>
</tr>
<tr>
<td>M13-099 (TURQUOISE-II)</td>
<td>GT1, treatment-naive and treatment-experienced, with compensated cirrhosis (Child-Pugh A)</td>
<td>3-DAA + RBV for 12 weeks vs 24 weeks</td>
<td>380</td>
</tr>
<tr>
<td>M13-389 (PEARL-I)</td>
<td>GT1b, non-cirrhotic, treatment-naive</td>
<td>3-DAA + RBV vs 5-DAA for 12 weeks</td>
<td>179</td>
</tr>
<tr>
<td>M13-391 (PEARL-II)</td>
<td>GT1b, non-cirrhotic, treatment-experienced</td>
<td>3-DAA + RBV vs 5-DAA for 12 weeks</td>
<td>429</td>
</tr>
<tr>
<td>M15-002 (PEARL-IV)</td>
<td>GT1a, non-cirrhotic, treatment-naive</td>
<td>3-DAA + RBV vs 5-DAA for 12 weeks</td>
<td>305</td>
</tr>
</tbody>
</table>

Phase 3 Program Clinical Data: Efficacy (SVR12)

- SAPPHIRE-I
- SAPPHIRE-E
- PEARL-I
- PEARL-II
- PEARL-IV
- TURQUOISE-II

Phase 3 Program Clinical Data: Safety

- D/C due to AEs
  - 1%
  - 1%
  - 0%
  - 0%
  - 0%
  - 0%
  - 0%
  - 0%
  - 0%
  - 0%
  - 0%
Sofosbuvir SVR 12 Across Treatment-Naïve Genotypes 1, 2, 3, 4, 5, 6

Ledipasvir/Sofosbuvir Background:

- **LDV/SOF:**

<table>
<thead>
<tr>
<th>Population</th>
<th>Duration</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN GT 1 Non cirrhotic</td>
<td>12* weeks</td>
<td>LDV 90mg/SOF 400 mg PO OD</td>
</tr>
<tr>
<td>TN GT1 cirrhotic</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>TE GT1 non cirrhotic</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>TE GT1 cirrhotic</td>
<td>24 weeks</td>
<td></td>
</tr>
</tbody>
</table>

* Can consider for 8 weeks in treatment naïve non cirrhotic with pre treatment HCV RNA < 6 million IU/mL

**Ledipasvir/Sofosbuvir:**

- **Ledipasvir**
  - Picomolar potency against HCV GT 1a and 1b
  - Effective against NS5B RAV S282T
  - Once daily, oral, 90 mg
- **Sofosbuvir**
  - Potent antiviral activity against HCV GT 1–6
  - High barrier to resistance
  - Once-daily, oral, 400 mg tablet
- **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)**

- ION-1: Treatment naïve: N = 865
- ION-2: Treatment experienced: N = 440
- ION-3: Treatment naïve: N = 647

N=1952 total patients

**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
• So let’s start treating then. But these new drugs are pretty expensive?

Program considerations

The treatment cascade: comprehensive HCV programming is essential

2.7-3.9 Million Infected
50% Detected
32-38% Referred
7-11% Treated

Asrani, Curr Gastroenterol Rep, 2014

Prioritization of treatment to those at highest risk of liver adverse event

Education and Evaluation

Recognize capacity issues associated with increased treatment demand

Ultimately provide access to all those requiring treatment

Identification and patient referral

Patient Stratification Plan for Birth Cohort

Patient Stratification Plan for At Risk/High Risk

Improved Models for High Risk Groups

HCV Care Model

CBC NEWS Prince Edward Island

$3M hepatitis C strategy announced by P.E.I. government

$3M hepatitis C strategy announced by P.E.I. government

Transiting to highly effective therapies for the treatment of chronic hepatitis C virus infection: A policy statement and implementation guideline
F4 prioritization decreases cost and liver complications

Markov HCV simulation model to model if phased fibrosis dependent treatment offers health economic value in screened baby boomers.

Targeting core transmitters

- Persons who inject drugs (PWID) account for 70-80% of incident infections in Canada.
- 50-80% will be seropositive after one year of IVDU.
- Estimated that average PWID will infect 20 persons, with majority of transmission event taking place in the first two years.
- 42.14% of opioid dependent persons in New Brunswick methadone maintenance clinic HCV+.

A Cost-Effectiveness Analysis for Prioritizing PWID / non-PWID Subpopulations for HCV Treatment

- HCV transmission and progression cost-effectiveness model to inform prioritization of HCV treatment; prioritizing cirrhotic patients was compared to prioritizing patients with IV drug use (PWID) and non/PWID with mild/moderate disease.
- In scenarios with low or medium HCV prevalence in PWID, it is cost-effective to prioritize treatment to PWID at earlier disease stages.
- These strategies likely prove to be cost-effective due to the substantial prevention benefits accrued by treating patients at an earlier stage of disease.

RECAP model of care

- Centre for Research, Education and Clinical Care of At-Risk Populations (RECAP).
- Nurse practitioner-led, inter-professional model of care for patients who are HCV-positive or at-risk of HCV acquisition.
- After optimization of clinical, mental, and social status, and with consideration to other comorbidities, it is determined whether the patient is a candidate for HCV treatment.
- Saint John based demonstration model to ensure clinical effectiveness with planned expansion to other areas in NB.

HCV Management Plan

- Identification and patient referral
- Education and evaluation
- Treatment
- Improved Models of Care for High Risk Groups
- Inclusive registration of all treated patients
- Patient satisfaction voluntary evaluation/linkage to direct and indirect healthcare costs
- Health’s mechanism for continued assessment and measurement and program improvement

HEAR Database

( Hepatitis C Positive and At-Risk Prospective Patient Database)

Intake - Patient
Intake - Physician
On/Off Treatment HEOR
Summary

• While disease prevalence is decreasing, complications of untreated chronic HCV will increase over the next two decades, as will healthcare expenditure.
• Cost of therapy is increasing, however cost of an SVR is decreasing.
• Versus rigid “F” restriction, maximal economic impact can be attained through dynamic programming which initially targets those with more advanced liver disease and core transmitters.
• Patient registries and outcome measures in the context of new therapies are essential to gauge real world clinical and health economic experience.

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