Interferon-free therapy for chronic hepatitis C

Prof. Alex Thompson
St. Vincent’s Hospital Melbourne, Australia
The University of Melbourne, Australia
Alice Springs, September, 2014

Disclosures

- Advisory board member – Gilead, Abbvie, Bristol-Myers Squibb (BMS), Janssen, Merck, and Roche
- Speaker - Gilead, Janssen, Merck, BMS, Abbvie
- PI - Gilead, Merck, Roche, BMS, Janssen, Achillion, Springbank
- Research / grant support – Gilead, Merck, BMS, Abbvie
- My presentation includes discussion of drugs which are not approved for clinical use

Evolution of HCV treatment

DAAs & the HCV lifecycle

IFN-free regimens in 2014*

Genotype 1 HCV

**Sofosbuvir + ledipasvir**: well tolerated

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall safety</td>
<td>160 (79)</td>
<td>160 (79)</td>
</tr>
<tr>
<td>AEs</td>
<td>160 (79)</td>
<td>160 (79)</td>
</tr>
<tr>
<td>Grade 3-4 AEs</td>
<td>4 (2)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1 (1)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Treatment-DCD</td>
<td>0 (0)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 3-4 laboratory abnormality</td>
<td>10 (6)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>Hb &lt;10 g/dL</td>
<td>0 (0)</td>
<td>20 (9)</td>
</tr>
<tr>
<td>Hb &lt;5.5 g/dL</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

No patient in either 12-week group discontinued drug owing to an adverse event. The most common adverse events were fatigue, headache, insomnia, and nausea.

**Sofosbuvir + ledipasvir (ION-1)**
SVR12 > 97% in treatment-naïve (TN)

**Sofosbuvir + ledipasvir (ION-3)**
8 wks sufficient for non-cirrhotic TN patients

**Sofosbuvir + ledipasvir (ION-2)**
Effective in treatment-experienced, TE

**Re-treatment with sofosbuvir**
Early data encouraging
ABT-450/r, ABT-267, ABT-333 + ribavirin (3D+R)

Sapphire-I (TN, non-cirrhotic): SVR12 > 95%

Paritaprevir/r, ombitasvir, dasabuvir + ribavirin (3D+R)

Sapphire-I (TN, non-cirrhotic): SVR12 > 95%

3D+R: well tolerated

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>3D + RBV</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amy AE</td>
<td>414 (87.5)</td>
<td>136 (73.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fatigue</td>
<td>104 (44.7)</td>
<td>45 (26.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Headache</td>
<td>150 (53.0)</td>
<td>42 (26.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea</td>
<td>122 (25.2)</td>
<td>23 (13.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pruritus</td>
<td>80 (16.9)</td>
<td>6 (3.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Insomnia</td>
<td>66 (14.0)</td>
<td>12 (7.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>65 (13.7)</td>
<td>11 (7.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Rash</td>
<td>51 (10.8)</td>
<td>9 (5.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

AEs were generally mild.

Discontinuation rate = 0.8% (2/473)

3D+R

Sapphire-II (TE, non-cirrhotic): SVR12 > 95%

Turquoise-II (cirrhotic): SVR12 > 90%

3D+R

Turquoise-II (cirrhotic): SVR12 > 90%

Discontinuation rate due to AEs = 2.1%

**Hallmark-Dual (HCV-1b): SVR12 > 80%**

- **Key eligibility criteria**
  - Daclatasvir + asunaprevir
  - Dual (HCV-1b): SVR12 > 80%

  

**Baseline RAVs reduce SVR12**

- Baseline NS5A/NS3 resistance associated variants – 76 / 637*
  - NS5A L31 / Y93
  - SVR12 = 28 / 73 (38%)
  - NS3 D168E
  - SVR12 = 2 / 4

- Virologic failure – n = 79*
  - 61 / 79: three variants detectable (NS5 L31, Y93 + NS3 D168)

**Sofosbuvir + simeprevir* HCV-Target Study: Phase 4 real world data**

**COSMOS (phase 2) - high SVR rates**

- Sofosbuvir + simeprevir*

  - Cohort 1 (n=80)
    - METAVIR F0 – 2
    - prior null responders to PR
  - Cohort 2 (n=87)
    - METAVIR F3 – 4
    - nulls / naive

**Sofosbuvir largely overcomes the Gt-1a – Q80K issue**

- All 3 relapsers were infected w HCV Gt-1a w detectable Q80K at baseline

**Sofosbuvir + simeprevir HCV-Target Study: Phase 4 real world data**

- Sofosbuvir largely overcomes the Gt-1a – Q80K issue
HCV-Target Study: SOF-SMV
Phase 4 real world data supports efficacy

Genotype 2/3 HCV

Sofosbuvir + RBV:
12 wks is enough for Gt 2 but not Gt 3

Sofosbuvir + RBV:
Gt 3 – 24 weeks is better than 12 wks

Pan-genotypic regimens?
One size fits all

Daclatasvir + Sofosbuvir ± RBV:
Phase 2 data show high SVR12 in Gt 1-3

Nelson, AASLD/EASL: Special Conference on Hepatitis C, New York City, Sep, 2014
Sofosbuvir + GS-5816 (NS5Ai): Phase 2 data show high SVR rates in all HCV Gt

Study Design (n = 154)

Where to from here?

- Clinical trials
  - Regimen optimization
  - Special populations
    - Decompensated liver disease, peri-Tx
    - (HIV), renal failure, haemoglobinopathies
    - Acute HCV, people who inject drugs (PWID)
  - Preventing transmission

- Real world challenges
  - Cost / access

IFN-free regimens beyond 2014

<table>
<thead>
<tr>
<th>Gilead, Abbvie, BMS, Merck, Achillion</th>
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<tbody>
<tr>
<td><strong>HCV genotype</strong></td>
</tr>
<tr>
<td><strong>TN</strong></td>
</tr>
<tr>
<td><strong>TE</strong></td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
</tr>
<tr>
<td><strong>HIV Co-infection</strong></td>
</tr>
<tr>
<td><strong>Special populations</strong></td>
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</tbody>
</table>

SOF +RBV pre-liver transplantation: Prevents recurrent HCV post-Tx

“pTVR12” (SVR12), n=44

Relationship between HCV recurrence and days continuously “TND” prior to transplant

All patients were wait-listed for HCC (low MELD)

24 weeks SOF + RBV therapy: Reverses liver complications

<table>
<thead>
<tr>
<th>Ascess</th>
<th>Hepatic encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>SOF+RBV</strong></td>
</tr>
<tr>
<td>Week 12</td>
<td>6</td>
</tr>
<tr>
<td>Week 24</td>
<td>5</td>
</tr>
</tbody>
</table>

Afdhal, EASL, 2014
Treating PWID reduces CHC prevalence

Impact increases with scale-up

* Assumes IFN-free DAA with 90% efficacy, 12 week duration

Conclusion: IFN-free regimens in 2014*

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<thead>
<tr>
<th>HCV genotype</th>
<th>Sofosbuvir + ledipasvir</th>
<th>Daclatasvir + asunaprevir</th>
<th>Sofosbuvir + simeprevir*</th>
<th>Sofosbuvir + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A/B</td>
<td>Y</td>
<td>Y</td>
<td>Y*</td>
<td>Y</td>
</tr>
<tr>
<td>1A/B</td>
<td>Y</td>
<td>Y</td>
<td>Y*</td>
<td>Y</td>
</tr>
<tr>
<td>1B</td>
<td>Y</td>
<td>Y</td>
<td>Y*</td>
<td>Y</td>
</tr>
<tr>
<td>1A/B*</td>
<td>12w</td>
<td>24w</td>
<td>12w*</td>
<td>2/3</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Y</td>
<td>Y*</td>
<td>Y*</td>
<td>Y</td>
</tr>
<tr>
<td>Duration</td>
<td>8-12w</td>
<td>12w</td>
<td>24w</td>
<td>12w*</td>
</tr>
<tr>
<td>SVR12</td>
<td>&gt; 95%</td>
<td>&gt; 95%</td>
<td>&gt; 90%*</td>
<td>&gt; 90%*</td>
</tr>
</tbody>
</table>

Pan-genotypic regimens are emerging (“one size fits all”)

Conclusion

IFN-free regimens should be the new SOC

- 12(1-24) week duration, simple regimens
- SVR12 > 90%*
- Well-tolerated, suitable for “difficult to treat” populations
- Low pill burden, less drug-drug interactions

URGENT access to these therapies is vital

- Life-saving for patients with decompensated liver disease
- Targeted use will reduce the HCV epidemic

HCV-free Australia?

“Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning”

Winston Churchill, 1942