Short Duration DAA Therapy for Hepatitis C: How Short Can We Go?

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HEPDART
Kona, HI
Disclosures

- Received research grants paid to the institution from Medimmune Inc, Merck Inc, Arbutus Pharmaceuticals and Gilead Sciences Inc.
Objective

To evaluate strategies employed to shorten duration of HCV therapy beyond 8 weeks
Rationale
Mechanism of HCV Clearance

Target cell → Death

Virions

Infected hepatocyte → Death/loss

DAA

Host Immunity
Addition of a 3rd DAA Improves Viral Kinetics

Potency of DAA Influences the Need for Host Immunity to Achieve SVR

Patients with IL28B CC haplotype have faster decline of HCV to SOF+RBV

Kohli A.... Kottilil S Hepdart 2013

No difference is observed when more potent LDV + SOF is used
HCV specific phenotype

- 25x10^6 CFSE labeled PBMC
- Genotype matched HCV peptides
- 48 hour incubation
- Flow cytometry

CD4
CD3
PD-1
Tim-3
CD57
CD8

CFSE low = proliferation
= antigen responsive

Live Dead
IL-2
IFN-γ
TNF-α
CTLA-4
Live cells and cells responding to antigen are gated for further analysis.

*Exclusion Dye

Cell division in response to HCV antigen
Enhanced Viral Suppression Improves Antiviral Immunity

A. SPARE (Sofosbuvir + Ribavirin)

![Graph showing Interferon γ Spots (Fold increase) over Baseline and End of Treatment for Relapser and SVR categories.]

Shrivastava S. Kottilil S. AASLD 2015
Precision Medicine for HCV

![Bar chart showing SVR 12 percentages for different IL28B genotypes.]

- High VL, IL28B non-CC: 88%
- Low VL, IL28B CC: 100%

Student's t-test, p = 0.001
Adherence to DAA therapy drops with duration

Petersen…Kottillil, Kohli et. al. Hepatology International 2015
Shortening Treatment Duration Saves Money

Veteran's Administration 2015: 254,000 patients with HCV; 20% cirrhosis

Per patient

Overall

$31,500

$3.15 \times 10^9
The Trials
## Short Duration HCV Therapy

<table>
<thead>
<tr>
<th>Combination</th>
<th>Duration (weeks)</th>
<th>Treatment-naive</th>
<th>Cirrhotic status</th>
<th>Sustained virological response (n [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir and odaLasvir (PROXY)</td>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Ledipasvir, sofosbuvir, GS-9669 (SYNERGY)</td>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>19 (95%)</td>
</tr>
<tr>
<td>Ledipasvir, sofosbuvir, GS-9451 (SYNERGY)</td>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>19 (95%)</td>
</tr>
<tr>
<td>Sofosbuvir, ledipasvir, ribavirin (ELECTRON)</td>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>Sofosbuvir, velpatasvir, voxilaprevir (formerly GS-9857; LEPTON)</td>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>Grazoprevir, elbasvir, sofosbuvir (C-SWIFT)</td>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>26 (87%)</td>
</tr>
<tr>
<td>Daclatasvir, asunaprevir, beclabuvir, sofosbuvir (FOURward)</td>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Sofosbuvir, velpatasvir, voxilaprevir (LEPTON)</td>
<td>6</td>
<td>No</td>
<td>Yes</td>
<td>20 (67%)</td>
</tr>
<tr>
<td>Ledipasvir, sofosbuvir, GS-9451 (SYNERGY)</td>
<td>6</td>
<td>No</td>
<td>Yes</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>Grazoprevir, elbasvir, sofosbuvir (C-SWIFT)</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>Sofosbuvir, velpatasvir, voxilaprevir (LEPTON)</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>Ledipasvir, sofosbuvir, GS-9451 (SYNERGY)</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Ledipasvir, sofosbuvir, GS-9451 (SYNERGY)</td>
<td>4</td>
<td>Yes</td>
<td>No</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Ledipasvir, sofosbuvir, GS-9451, GS-9669 (SYNERGY)</td>
<td>4</td>
<td>Yes</td>
<td>No</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Grazoprevir, elbasvir, sofosbuvir (C-SWIFT)</td>
<td>4</td>
<td>Yes</td>
<td>No</td>
<td>10 (32%)</td>
</tr>
<tr>
<td>Sofosbuvir, velpatasvir, voxilaprevir (LEPTON)</td>
<td>4</td>
<td>Yes</td>
<td>No</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Daclatasvir, asunaprevir, beclabuvir, sofosbuvir (FOURward)</td>
<td>4</td>
<td>Yes</td>
<td>No</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Sofosbuvir, ledipasvir, asunaprevir (SODAPI)</td>
<td>3</td>
<td>Yes (50%)</td>
<td>No</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Sofosbuvir, daclatasvir, simeprevir (SODAPI)</td>
<td>3</td>
<td>Yes (67%)</td>
<td>No</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Sofosbuvir, daclatasvir, asunaprevir (SODAPI)</td>
<td>3</td>
<td>Yes (83%)</td>
<td>No</td>
<td>6 (100%)</td>
</tr>
</tbody>
</table>

The SODAPI study was a clinical trial of response-guided therapy.
Predictors of SVR

- Baseline HCV Viral load
- HCV genotype 1b
- Absence of RAVs
Efficacy and safety of 3-week response-guided triple direct-acting antiviral therapy for chronic hepatitis C infection: a phase 2, open-label, proof-of-concept study

George Lau*, Yves Benhamou, Guofeng Chen, Jin Li, Qing Shao, Dong Ji, Fan Li, Bing Li, Jialiang Liu, Jinlin Hou, Jian Sun, Cheng Wang, Jing Chen, Vanessa Wu, April Wong, Chris L P Wong, Stella T Y Tsang, Yudong Wang, Leda Bassit, Sijia Tao, Yong Jiang, Hui-Mien Hsiao, Ruian Ke, Alan S Perelson, Raymond F Schinazi*
Sofosbuvir (SOF, nucleotide NS5B inhibitor) 400 mg once daily
Ledipasvir (LDV, NS5A inhibitor) 90 mg once daily
Daclatasvir (DCV, NS5A inhibitor) 60 mg once daily
Simeprevir (SMV, a protease/ NS3/4 inhibitor) 150 mg once daily
Asunaprevir (ASV, a protease/ NS3/4 inhibitor) 100 mg twice daily

GT-1b Non-cirrhotic Chinese Patients

Patient randomly assigned

Group 1: SOF/LDV+ASV
NC=6

Day 0 3521 1052
GT-1b
Non-
cirrhotic
Chinese
Patients

Group 2: SOF+DCV+SMV
NC=6

Group 3: SOF+DCV+ASV
NC=6

Plasma HCV RNA < 500 IU/ml by Day 2

Follow up

SODAPI Study Flow

Day 21 35 105
Follow up

Follow up

Follow up
SODAPI Viral Measurements

% Patients with VL<25 IU/mL

- **Day 2**: 16% (SOF/LDV/ASV), 33% (SOF/DCV/SMV)
- **Day 4**: 83% (SOF/LDV/ASV), 0% (SOF/DCV/SMV)
- **Day 7**: 100% (SOF/LDV/ASV), 67% (SOF/DCV/SMV)
- **Week 2**: 100% (SOF/LDV/ASV), 100% (SOF/DCV/SMV)
- **Week 3**: 100% (SOF/LDV/ASV), 100% (SOF/DCV/SMV)
- **SVR4**: 100% (SOF/LDV/ASV), 100% (SOF/DCV/SMV)
- **SVR12**: 100% (SOF/LDV/ASV), 100% (SOF/DCV/SMV)
Future Considerations
Effective Retreatment Strategy for Failures: SYNERGY

<table>
<thead>
<tr>
<th>Time</th>
<th>% of Patients with HCV RNA &lt; LLOQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>64.7% (22/34)</td>
</tr>
<tr>
<td>EOT</td>
<td>88.2% (30/34)</td>
</tr>
<tr>
<td>Week 12</td>
<td>94.1% (32/34)</td>
</tr>
<tr>
<td>Week 16</td>
<td>91.2% (31/34)</td>
</tr>
<tr>
<td>Week 20</td>
<td>91.2% (31/34)</td>
</tr>
<tr>
<td>Week 24</td>
<td>96.9% (31/32)</td>
</tr>
</tbody>
</table>

- 2 patients withdrew consent
- 1 patient relapsed
Distribution of HCV genotypes

Increasing Potency is Possible

Infection

Target cell

Virions

Infected hepatocyte

Death

Clearance

Death/loss

Host Immunity

DAA
AL-335 604 Study

SVR (%)

- Genotype 1:
  - 6 weeks: 100%
  - 8 weeks: 100%

- Genotype 3:
  - 6 weeks: 75%
  - 12 weeks: 75%

Gane EJ et al. AASLD 2017
Potent Non Nucleoside Analog

- HCV RNA viral load decline of 3 logs by 48 hours
- After the NNI treatment, the viral load levels were slowly increased
- Drug resistance analysis ongoing

![Graph showing viral load change from baseline](chart.jpg)

- 400 mg QD
- 200 mg BID

Lee S et al. APASL 2017
People Who Inject Drugs

Increasing incidence of HCV among young adults (USA)

People Who Inject Drugs

Overhus A. et al. AASLD 2016
Incarceration

1.9 million HCV + incarcerated persons are reservoir for new infections (USA)

Conclusions

- Shortening HCV therapy beyond 4 weeks in targeted population is possible and should be further explored.

- Factors influencing high SVR with short duration combination DAA therapy include low baseline HCV VL, absence of RAVs, Genotype 1b, being female, and having IL28B CC haplotype.

- For treatment of all patients, newer DAAs that may be more potent and/or have longer half life need to be studied in the future.

- Co-ordinated global strategy to explore short duration therapy for hepatitis C is warranted.
Acknowledgments

- Institute of Human Virology
  - Eleanor Wilson MD
  - Lydia Tang MD
  - Amy Nelson RN
  - Jennifer Hoffmann CRNP
  - Shikha Shrivastava Ph.D

- NIH DC-Program for AIDS Progress
  - Sarah Kattakuzhy MD
  - Elana Rosenthal MD
  - Poonam Mathur DO, MPH

- Institute for Liver Health, Phoenix
  - Anita Kohli MD

- NIH
  - Henry Masur MD

- Dalhousie University, Canada
  - Lisa Barrett MD, Ph.D

- Humanities and Health Medical Group
  - George Lau MD
  - Vanessa Wu

- CoCrystal Pharmaceuticals
  - Sam Lee Ph.D
  - Luz Pascual

- Emory University
  - Raymond Schinazi Ph.D

- Gilead Sciences Inc.
  - Anu Osinusi MD

Patients