The Role of New Combination Therapies without Interferon for Chronic HCV Infection

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Outline

- Introduction
- Interferon-based Therapy
- New Combination Therapies without Interferon
- The Role of New Combination Therapies
- Summary
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Age-Specific HCV Worldwide Prevalence

- 122 millions (2.3%) in 1990 ➔ 185 millions (2.8%) in 2005
- > 111 million HCV-infected people reside in East, South, and South East Asia

HCV control is a critical issue in Asia

Adapted from Mohd Hanafiah et al., Hepatology 2013; 57: 1333
Hepatitis C Virus Prevalence in Asian Pacific Region

Sievert et al, Liver Int 2011; 31 (Suppl 2): 61
Natural History of HCV Infection

Exposure (Acute phase)

- Resolved
- Chronic
  - Stable
  - Slowly Progressive

Chronic

- Cirrhosis
  - HCC
  - Transplant
  - Death

Percentages:

- 20%
- 60-80%
- 80%
- 20%
- 75%
- 25%

Sources:

Alter MJ. Semin Liver Dis 1995; 15: 5-14
Management of Hepatitis C: NIH Consensus Statement 1997
Potential Benefits of Sustained Virologic Response (SVR)

* Decreased infectivity
* Decreased risk for cirrhosis or decompensation
* Decreased risk for hepatocellular carcinoma
* Improved survival
* Improved quality of life

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Standard IFN α-2b as Initial Therapy for Chronic Hepatitis C

McHutchison et al. NEJM 1998; 339: 1485
Poynard et al. Lancet 1998; 352: 1426
SVR to 24-Week IFN/Ribavirin Combination Therapy and IFN Monotherapy in CHC Patients

Lai et al. Gastroenterology 1996; 111: 1307
Treatment with PegIFN Plus Ribavirin is the Standard of Care

- Peg-IFNα-2a + RBV
- Peg-IFNα-2b + RBV

All HCV genotypes

Optimal Treatment Regimen
Genotype-Guided Therapy

AASLD 2004 recommendation
- 48 weeks of PegIFN plus SD of RBV for HCV-1/4
- 24 weeks of PegIFN plus LD of RBV for HCV-2/3

Peg-IFNα-2a 180 mcg/w + RBV

LD = RBV 800 mg/day
SD = RBV 1000–1200 mg/day

# Table 1: DAAs and HTAs in Clinical Development at the Beginning of 2014

<table>
<thead>
<tr>
<th>Agent class</th>
<th>Generation</th>
<th>Compound</th>
<th>Manufacturer</th>
<th>Phase of clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3-4A protease inhibitors</td>
<td>First-wave, first-generation</td>
<td>Telaprevir</td>
<td>Vertex, Janssen, Mitsubishi</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bocceprevir</td>
<td>Merck</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simeprevir</td>
<td>Janssen</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>Second-wave, first-generation</td>
<td>Faldaprevir</td>
<td>Boehringer-Ingelheim</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asunaprevir</td>
<td>Bristol-Myers Squibb</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ABT-450/r</td>
<td>Abbvie</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Danoprevir/r</td>
<td>Roche</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sovaprevir</td>
<td>Achillion</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vedoprevir</td>
<td>Gilead</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IDX320</td>
<td>Idenix</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaniprevir</td>
<td>Merck</td>
<td>III (Japan)</td>
</tr>
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<td></td>
<td>Second-generation</td>
<td>ACH-2584</td>
<td>Achillion</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Nucleoside/nucleotide analogues</td>
<td>Sofosbuvir</td>
<td>Gilead</td>
<td>Approved</td>
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<td></td>
<td>VA-1052</td>
<td>Vertex</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Nucleoside analogue</td>
<td>Mericitabine</td>
<td>Roche</td>
<td>II</td>
</tr>
<tr>
<td>Non-nucleoside inhibitors of the HCV RdRp</td>
<td>Thumb domain I inhibitors</td>
<td>BMS-791325</td>
<td>Bristol-Myers Squibb</td>
<td>III</td>
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<tr>
<td></td>
<td></td>
<td>TMC647055</td>
<td>Janssen</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Thumb domain II inhibitors</td>
<td>Lomibuvir</td>
<td>Vertex</td>
<td>II</td>
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<tr>
<td></td>
<td></td>
<td>GS-9669</td>
<td>Gilead</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Palm domain I inhibitors</td>
<td>Dasabuvir</td>
<td>Abbvie</td>
<td>III</td>
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<tr>
<td></td>
<td></td>
<td>ABT-072</td>
<td>Abbvie</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Setrobuvir</td>
<td>Roche</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>NS5A inhibitors</td>
<td>Daclatasvir</td>
<td>Bristol-Myers Squibb</td>
<td>III</td>
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<tr>
<td></td>
<td></td>
<td>Ledipasvir</td>
<td>Gilead</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ombitasvir</td>
<td>Abbvie</td>
<td>III</td>
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<td>PPI-668</td>
<td>Presidio</td>
<td>II</td>
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<td></td>
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<td>PPI-461</td>
<td>Presidio</td>
<td>II</td>
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<td></td>
<td>ACH-2928</td>
<td>Achillion</td>
<td>II</td>
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<td></td>
<td>GSK2336805</td>
<td>GlaxoSmithKline</td>
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<td></td>
<td>BMS824393</td>
<td>Bristol-Myers Squibb</td>
<td>II</td>
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<tr>
<td></td>
<td>Second-generation</td>
<td>Samatasvir</td>
<td>Idenix</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MK-8742</td>
<td>Merck</td>
<td>II</td>
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<td></td>
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<td>ACH-3102</td>
<td>Achillion</td>
<td>II</td>
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<tr>
<td></td>
<td></td>
<td>GS-5816</td>
<td>Gilead</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Cyclophilin inhibitors</td>
<td>Alisporivir</td>
<td>Novartis</td>
<td>II</td>
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<tr>
<td></td>
<td></td>
<td>SCY-635</td>
<td>Scynexis</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Antagonist of miRNA-122</td>
<td>Miravirsen</td>
<td>Santaris</td>
<td>II</td>
</tr>
</tbody>
</table>
SVR Rates with BOC and TVR in GT1 Treatment Naïve and Experienced Patients

- Treatment-naive patients
  - ADVANCE/SPRINT-2/ILLUMINATE: 63–75%
  - ADVANCE/SPRINT-2: 38–44%

- Treatment-experienced patients
  - RESPOND-2/REALIZE: 59–66%
  - RESPOND-2/REALIZE: 17–21%

Challenges of 1\textsuperscript{st} Wave Protease Inhibitors

- **Efficacy:** - Very dependent on the IFN response (W4 VR)
  - only 30% for NR, 15% for prior NR/cirrhotic

- **Resistance-associated Variants:** especially for HCV-1a

- **Tolerability:** Additional AEs beyond pegIFN/RBV (SAE > 30% in LC)

- **Regimens**
  - Complicated (lead-in, RGT, FDA/EU, TN/TE, futility)
  - pill burden, treatment duration, adherence

- **Drug-Drug Interactions**
  - Many with both agents to common drugs (Statin, SSRI, Sildenafil)
  - > 50% FDA-approved drugs are either substrates or inhibitors of CYP3A4 (www.hep-druginteractions.org)
### QUEST-1: Virologic Response to Simeprevir + P/R Treatment

#### Virologic Outcomes

<table>
<thead>
<tr>
<th>Time</th>
<th>SMV + P/R (n/N)</th>
<th>P/R (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>202/254</td>
<td>210/264</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>Week 12</td>
<td>210/130</td>
<td>65/28</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>91</td>
</tr>
</tbody>
</table>

#### SVR12 by RGT Group

- **85% of pts in SMV arm met RGT criteria**

  - **SMV Arm: Total Duration of RGT**
    - 24 Wks: 203/224
    - 48 Wks: 6/28

  - **SVR12 (%)**
    - 24 Wks: 91
    - 48 Wks: 21

*Jacobson et al. Lancet 2014; 384: 403*
NEUTRINO: SVR12 with Sofosbuvir + P/R
According to Genotype & Fibrosis Level

SVR12 According to Genotype

- GT 1: 89% (261/292)
- GT 4: 96% (27/28)
- GT 5,6: 100% (7/7)

SVR12 According to Fibrosis Level

- No Cirrhosis: 92% (252/273)
- Cirrhosis: 80% (43/54)

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24-Wk Daclatasvir (NS5AI) + Asunaprevir (PI) in HCV-1 Null-responders, Ineligible/Intolerant Patients

<table>
<thead>
<tr>
<th>AI447-011</th>
<th>Daclatasvir 60mg/d + Asunaprevir 600 mg BID  (n = 11)</th>
<th>follow-up x 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null-R Arm</td>
<td></td>
<td>Null-G1a</td>
</tr>
<tr>
<td>A1</td>
<td></td>
<td>Null-G1b</td>
</tr>
<tr>
<td>AI447-017</td>
<td>Daclatasvir 60mg/d + Asunaprevir 600 mg BID* (n = 10)</td>
<td></td>
</tr>
<tr>
<td>sentinel cohort</td>
<td></td>
<td>Null-R</td>
</tr>
<tr>
<td>Null-R2</td>
<td></td>
<td>Ineligible Intolerant</td>
</tr>
<tr>
<td>AI447-017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese G1b cohort</td>
<td>Daclatasvir 60mg/d + Asunaprevir 600 mg BID* (Null-R n=21; ineligible/intolerant n=22)</td>
<td>follow-up x 24 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

24-week treatment

SVR_{12}  SVR_{24}

*ASV initially 600 mg BID in sentinel cohort of 10 null responders, reduced to 200 mg BID during treatment

• most patients with virologic failure had pre-existing NS5A-Y93H polymorphisms

SVR12 Rates in HCV 2/3 Patients Treated with Sofosbuvir & Ribavirin

A (G2)

- Naïve
  - 12 weeks: 95% (69/73)
  - 16 weeks: 93% (68/73)
  - Expressed
  - 12 weeks: 82% (32/39)
  - 16 weeks: 89% (31/35)

B (G2)

- No cirrhosis
  - FISSION
    - 12 weeks: 97% (59/61)
    - 16 weeks: 83% (10/12)
  - FUSION
    - 12 weeks: 90% (26/29)
    - 16 weeks: 92% (24/26)

- Cirrhosis
  - No cirrhosis
    - 12 weeks: 60% (6/10)
    - 16 weeks: 78% (7/9)

C (G3 Naïve)

- No cirrhosis
  - 12 weeks (FISSION): 61% (88/145)
  - 24 weeks (VALENCE): 34% (13/38)
  - Cirrhosis
    - 12 weeks (FISSION): 93% (86/92)
    - 24 weeks (VALENCE): 92% (12/13)

D (G3 Experienced)

- No cirrhosis
  - 12 weeks (FUSION): 37% (14/38)
  - 16 weeks (FUSION): 63% (25/40)
  - 24 weeks (VALENCE): 87% (87/100)
  - Cirrhosis
    - 12 weeks (FUSION): 61% (5/26)
    - 16 weeks (FUSION): 60% (14/23)
    - 24 weeks (VALENCE): 60% (27/45)

Pawlotsky PM. Gastroenterology 2014; 146: 1176
SVR12 Rates in HCV G1 Patients Treated with Sofosbuvir and Ledipasvir FDC

A (G1 Naïve)

- 98% (209/214) Sofosbuvir + ledipasvir + ribavirin 12 weeks (ION-1)
- 97% (211/217) Sofosbuvir + ledipasvir 12 weeks
- 94% (202/215) Sofosbuvir + ledipasvir + ribavirin 8 weeks (ION-3)
- 93% (201/216) Sofosbuvir + ledipasvir + ribavirin 8 weeks
- 95% (205/216) Sofosbuvir + ledipasvir + ribavirin 12 weeks

B (G1 Experienced)

- 94% (102/109) Sofosbuvir + ledipasvir + ribavirin 12 weeks (ION-2)
- 96% (107/111) Sofosbuvir + ledipasvir + ribavirin 12 weeks
- 99% (108/109) Sofosbuvir + ledipasvir + ribavirin 24 weeks
- 99% (110/111) Sofosbuvir + ledipasvir + ribavirin 24 weeks

No ribavirin | Ribavirin
--- | ---

Pawlotsky PM. Gastroenterology 2014; 146: 1176
SVR12 Rates in Taiwanese G1 & G2 CHC Patients Treated with Sofosbuvir-based Therapy

Genotype 1: LDV/SOF 12 Weeks

- Overall: 98%
- TN: 100%
- TE: 95%
- No Cirrhosis: 97%
- Yes Cirrhosis: 100%
- Treatment Experience: 83%
- Cirrhosis: 74%
- TE: 9%

Genotype 2: SOF + RBV 12 Weeks

- Overall: 100%
- TN: 100%
- TE: 100%
- No Cirrhosis: 100%
- Yes Cirrhosis: 100%
- Treatment Experience: 87%
- Cirrhosis: 74%
- TE: 43%
- Yes Cirrhosis: 13%

Chuang et al. APASL 2015
Sofosbuvir + Daclatasvir in Tx-Naive Pts and PI Failures with GT1 HCV Infection

COSMOS: Sofosbuvir + Simeprevir ± RBV in Tx-Naive and Tx-Experienced GT1 Pts

- No breakthrough on therapy, 6 relapses, 9 nonvirologic failures
- Efficacy of 12 wks similar to 24 wks; RBV provided no additional benefit
- Recently FDA approved: 12 wks in noncirrhotics, 24 wks for cirrhotics; no RBV

Lawitz et al. Lancet 2014; 384: 1756
SVR12 in HCV G1 Patients of SAPPHIRE-I, II, PEARL-II, III, IV, and TURQUOISE-II Phase III Trials
(Combination Treatment with ABT-450/r, Ombitasvir, and Dasabuvir, with or without Ribavirin)

Pawlotsky PM. Gastroenterology 2014; 146: 1176
HALLMARK-DUAL: SVR12 with Daclatasvir + Asunaprevir in GT1b HCV

- Breakthrough: 9 (4%) treatment naive, 26 (13%) nonresponders, 20 (9%) IFN ineligible/intolerant
- Relapse: 5 (3%) treatment naive, 7 (4%) nonresponders, 12 (6%) IFN ineligible/intolerant
- 28 of 73 patients with NS5A-L31 and/or Y93 variants at baseline achieved SVR12

<table>
<thead>
<tr>
<th>SVR12, % (n/N)</th>
<th>Daclatasvir + Asunaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>(182/203)</td>
</tr>
<tr>
<td>Null responders</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>(98/119)</td>
</tr>
<tr>
<td>Partial responders</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>(68/84)</td>
</tr>
<tr>
<td>All IFN ineligible/intolerant</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>(192/235)</td>
</tr>
<tr>
<td>Advanced fibrosis/cirrhosis with thrombocytopenia</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>(56/77)</td>
</tr>
</tbody>
</table>

Manns et al. Lancet 2014; 384: 1597
UNITY-1 and 2 Studies: Daclatasvir/ Asunaprevir/ Beclabuvir for non-Cirrhotic & Cirrhotic Patients with GT 1 HCV Infection


Asselah T & Marcellin P. Liver Int 2015; 35 (Suppl. 1): 56
C-WORTHY (Treatment-Naïve Cirrhotics and Null): Efficacy for Cirrhotic Patients & Virologic Failure

Nine of 253 (3.6%) treated patients experienced virologic failure:
• 7 patients: relapsed (6 GT1a and 1 GT1b)
• 2 patients: breakthrough (1 GT1a and 1 GT1b)

<table>
<thead>
<tr>
<th>Virologic failure</th>
<th>Cirrhosis</th>
<th>+ RBV (n = 129)</th>
<th>No RBV (n = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral breakthrough</td>
<td>Yes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Viral relapse</td>
<td>Yes</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

- 5/5 (100%) patients with baseline NS3 R155K or D168A RAVs by population sequencing achieved SVR4/8
- 27/33 (82%) patients with baseline NS5A 30, 31, and 93 RAVs by population sequencing achieved SVR4/8
- Signature RAVs detected by population sequencing at failure
  - NS3: Y56H, D168A, 156A/G/V
  - NS5A: Q30R/Q

* One G1b failure was null-cirrhotic
** One failure was a motor vehicle accident
Excludes patients who have not yet reached FU or who are neither G1a or G1b

TN: treatment-naïve

Lawitz et al. EASL 49th Annual Meeting, 2014
C-SWIFT Study: MK-5172 + MK-8742 + SOF in Treatment-Naïve Patients with HCV GT1

Fig. 5. C-SWIFT study: MK-5172 + MK-8742 + Sofosbuvir in Treatment-naïve Patients with HCV GT1, with or without Cirrhosis for Durations of 4, 6 or 8 weeks (reference: Lawitz et al. Hepatology 2014; LB-33).

Asselah T & Marcellin P. Liver Int 2015; 35 (Suppl. 1): 56
Safety and DDIs with SOF/LDV

- **Safety/tolerability**[^1]
  - Treatment-related AEs: 45% SOF/LDV vs 71% SOF/LDV + RBV
  - Without RBV:
    - < 1% d/c due to AEs
    - < 1% serious AEs
    - Headache, fatigue: ~ 20%
    - Nausea, diarrhea: ~ 8% to 10%
    - Almost no anemia

- **DDIs**[^2]
  - St John’s wort
  - Rifampin
  - Acid reducing agents: high pH reduces LDV absorption
  - Statins: coadministration with rosvastatin not recommended
  - Seizure meds: almost all contraindicated
  - Digoxin: be careful—may increase levels
  - ARVs: most okay; careful with TDF and check them all

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[^1]: Alqahtani et al. AASLD 2014. Abstract 1944
## Safety and DDIs with 3 DAAs ± RBV

<table>
<thead>
<tr>
<th>Event, %</th>
<th>3 DAAs + RBV</th>
<th>3 DAAs</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>84</td>
<td>75</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Serious AE</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Headache</td>
<td>25</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>9</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>6</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10 g/dL</td>
<td>7</td>
<td>0</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Bilirubin &gt; 3 x ULN</td>
<td>5</td>
<td>0.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

- DDIs: relatively similar to first-generation PIs (CYP3A) → check the label and other resources (e.g., University of Liverpool Web site)

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Treatment Options for GT4 HCV

IFN-Based Therapy

- SOF + P/R in Tx-Naive Pts\(^1\)
  - SVR12 (%): 96
  - 12 Wks: 27/28

- SMV + P/R in Tx-Naive and Tx-Exp’d Pts\(^2\)
  - SVR12 (%): 65
  - 12 Wks: 70/107

- SOF + RBV in Tx-Naive and Tx-Exp’d Pts\(^3\)
  - SVR12 (%): 77
  - 12 Wks: 40/52
  - 24 Wks: 46/51

All-Oral Therapy

- Other options: SOF + SMV; no data but should work

Treatment Options for GT4 HCV

SYNERGY: SOF/LDV x 12 Wks\textsuperscript{[1]}

\begin{tabular}{|c|c|}
\hline
SVR4 & 20/21 \\
\hline
SVR12 & 19/20 \\
\hline
\end{tabular}

\begin{tabular}{|c|c|}
\hline
< ILOQ (%) & 95 \\
\hline
\end{tabular}

PEARL-I: Paritaprevir/RTV/Ombitasvir ± RBV x 12 Wks\textsuperscript{[2]}

\begin{tabular}{|c|c|}
\hline
2 DAAs & 91 \\
\hline
2 DAAs + RBV & 100 \\
\hline
\end{tabular}

\begin{tabular}{|c|c|}
\hline
Naive Pts & 40/44 \\
\hline
P/R Failure & 42/42 \\
\hline
2 DAAs + RBV & 49/49 \\
\hline
\end{tabular}

\begin{tabular}{|c|c|}
\hline
SVR12 (%) & 100 \\
\hline
\end{tabular}

Outline

- Introduction
- Interferon-based Therapy
- New Combination Therapies without Interferon
- The Role of New Combination Therapies
- Summary
Perfectovir(s) ?
Requirements for HCV Therapy

- SVR > 90%
- Toxicity
- Tolerability
- Short duration
- High barrier to resistance
- One size fits all: pangenotypic
- No drug–drug interactions
- Low pill burden
Perfectovir(s) ?

Nearly!
For DAAs Affordable or Generic Drugs Available Countries
## Recommended Regimens for Treatment-Naïve GT1 HCV Pts

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Noncirrhotic</th>
<th>Compensated Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regimen</td>
<td>Duration, Wks</td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td>LDV/SOF</td>
<td>12*</td>
</tr>
<tr>
<td>GT1a</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1b</td>
<td>OMV/PTV/RTV + DSV</td>
<td>12</td>
</tr>
<tr>
<td>GT1a</td>
<td>SMV + SOF ± RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1b</td>
<td>SMV + SOF</td>
<td>12</td>
</tr>
</tbody>
</table>

* Shorter course can be considered in pts with pretreatment HCV RNA < 6 million IU/mL at provider’s discretion but should be done with caution.

AASLD/IDSA HCV Guidelines
# Recommended Regimens for Treatment-Experienced GT1 HCV Pts

<table>
<thead>
<tr>
<th>Population</th>
<th>Noncirrhotic</th>
<th>Compensated Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regimen</td>
<td>Duration, Wks</td>
</tr>
<tr>
<td>Prior PegIFN/RBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td>LDV/SOF</td>
<td>12</td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT1a</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1b</td>
<td>OMV/PTV/RTV + DSV</td>
<td>12</td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td>SMV + SOF ± RBV</td>
<td>12</td>
</tr>
<tr>
<td>Prior SOF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td>Defer therapy</td>
<td></td>
</tr>
<tr>
<td>Prior PI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td>LDV/SOF</td>
<td>12</td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AASLD/IDSA HCV Guidelines
Recommended Regimens for GT4

- Recognizing that data are limited, AASLD/IDSA guidance makes these recommendations:
  - LDV/SOF for 12 wks
  - OMV/PTV/RTV + RBV for 12 wks
  - SOF + RBV for 24 wks
    - Recommended in treatment-experienced and as alternative for treatment-naive pts: SOF + RBV + pegIFN for 12 wks
    - Alternative for treatment-naive pts: SOF + SMV ± RBV for 12 wks
## 2014 AASLD-IDSA HCV Guidelines - HCV-2, 3 -

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended</th>
<th>Alternative</th>
<th>NOT Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment naive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 2 | SOF + RBV x 12wk | None | • PEG + RBV  
• TVR, BOC, SMV  
• Any single DAA |
| 3 | SOF + RBV x 24wk | SOF + PEG/RBV x 12wk | • PEG + RBV  
• TVR, BOC, SMV  
• Any single DAA |
| **Failed to prior PegIFN/RBV** | | | |
| 2 | SOF + RBV x 12wk | SOF + PEG/RBV x 12wk | • PEG + RBV  
• TVR, BOC, SMV  
• Any single DAA |
| 3 | SOF + RBV x 24wk | SOF + PEG/RBV x 12wk | |
One Strategy for All Countries?
Standard of Care

- Available
- Acceptable
- Accessible
- Affordable
DAAs for CHC Therapy
not yet Widely Available in Asia

The data of DAAs for Asian CHC patients are limited
Costs for FDA-Approved DAAs

- **Boceprevir** (Victrelis): $26,400 for 24 weeks, $35,200 for 32 weeks, and $48,400 for 44 weeks
- **Telaprevir** (Incivek): $49,200 for 12 weeks
- **Simeprevir** (Olysio): $66,360 for 12 weeks
- **Sofosbuvir** (Sovaldi): $84,000 for 12 weeks
- **SOF & Ledipasvir** (Harvoni): $94,500 for 12 weeks
- **Daclatasvir & Asunaprevir**: $27,000 for 24 weeks
- **3D Regimen** (Viekira pak): $83,319 for 12 weeks

* The costs do not include the other medications for combination therapy
* The cost for a 48-week course of **pegylated interferon and ribavirin** is approximately $10,000 in Taiwan (reimbursed by national health insurance).

http://www.hepatitisc.uw.edu/page/treatment/drugs
For DAAs **Unaffordable** and **Generic Drugs** Unavailable Countries
Combination therapy with **PegIFN** and **Ribavirin** is still the SOC for treatment of CHC (the situation in most of Asian countries)
For the Countries

DAAs Available

but only with Limited Resources

(Generic Drugs not Available)
12. In chronic HCV genotype 1 infection, the following apply: (I)

- Treatment with peginterferon and ribavirin for 48 weeks is recommended.

- In patients who achieve an RVR at week 4, treatment can be discontinued after 24 weeks if the HCV RNA at baseline is <400,000 IU/mL.

- In patients who achieve a complete EVR at week 12, treatment should be continued up to 48 weeks.

- In patients who do not achieve an EVR at week 12, but show a significant reduction in HCV RNA levels (partial EVR) and negativity of HCV RNA at week 24 (late virological response, LVR), treatment may be continued up to 72 weeks.

Omata et al. Hepatol Int 2012; 6: 409
SVR Rates with 48-week PegIFN Plus Ribavirin in Genotype 1 (≈50%)

RVR is a Strong Predictor of SVR in HCV-1

Post hoc/retrospective analysis

PEGASYS® 180 µg plus COPEGUS®

LD = RBV 800 mg/day; SD = RBV 1000–1200 mg/day;
RVR = HCV RNA <50 IU/mL at week 4

Jensen et al. Hepatology 2006; 43: 954
HCV-1 patients with an LVL and RVR

Equal Efficacy with 24-week PegIFN/RBV

Data from 5 studies in East & West population

RVR = HCV RNA <50 IU/mL at wk 4; LVL (low viral load) = \(1 \leq 400,000; \ 4 \leq 600,000; \ 2,3 \leq 800,000\) IU/mL

High SVR Rates with 24-Wk PegIFN Plus Ribavirin in Genotype 2/3 (~83%)

24-week treatment duration

- Peg-IFNα-2a + RBV
- Peg-IFNα-2b + RBV

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>SVR (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Hadziyannis</td>
<td>84%</td>
<td>96</td>
</tr>
<tr>
<td>2004</td>
<td>Von Wagner</td>
<td>80%</td>
<td>71</td>
</tr>
<tr>
<td>2005</td>
<td>Zeuzem</td>
<td>95%</td>
<td>19</td>
</tr>
<tr>
<td>2004</td>
<td>Zeuzem</td>
<td>81%</td>
<td>224</td>
</tr>
<tr>
<td>2005</td>
<td>Mangia</td>
<td>76%</td>
<td>70</td>
</tr>
</tbody>
</table>

Equal Efficacy between 16 and 24-Wk Groups – HCV-2

Intention-to-treat analysis

Yu, Chuang, et al, Gut 2007; 56: 553
Racial Difference of SVR Rates in HCV-1/4

PegIFN + SD RBV for 48 weeks

Some data from individual studies, not all direct head-to-head comparison

Yu & Chuang. J Gastroenterol Hepatol 2009
Percentage of SVR by Genotypes of rs12979860

C/C vs. T/T   OR: 2.0 (95% CI: 1.8-2.3)   OR: 3.0 (95% CI: 1.9-4.7)   OR: 2.1 (95% CI: 1.4-3.2)

Ge et al, Nature 2009; 461: 399
IL-28B SNP & RVR on SVR in HCV-1

Thompson et al.
Gastroenterol 2010
IDEAL Caucasians
N=1171

Huang, Chuang, Yu, et al.
J Hepatol 2012
Taiwan HCV-1,
Tx for 24 wks
N= 226

Huang, Chuang, Yu, et al.
Antiviral Res 2012
Taiwan HCV-1,
Tx for 48 wks
N= 182
Treatment-experienced HCV patients Retreatment with PegIFN/RBV in Taiwan

48w PegIFN/RBV for HCV-1; 24w PegIFN/RBV for HCV-2/3

IL-28B rs8099917 genotype

Treatment-experienced HCV-2 patients
Retreatment with PegIFN/RBV in Asia

Regimens of retreatment:
24w PegIFN/RBV for HCV-2/3

SVR (%)

N =

Previous null responders

Previous relapsers

Retreatment with SOC for previous relapsers is encouraged

HCV Practice Recommendation for IFN-eligible Naïve Patients in Asia-Pacific Countries with DAA Available

HCV, hepatitis C virus; DAA, direct acting antivirals; BL, baseline; W, treatment week; LVL, low HCV viral loads; HVL, high HCV viral loads; RVR, rapid virologic response, HCV RNA undetectable at week 4; P or PegIFN, peginterferon; R or RBV, ribavirin.

Dot line indicated option of choice, based on cost-effectiveness of available DAA regimens

* For areas with only boceprevir/PR, telaprevir/PR, simeprevir/PR or daclatasvir/PR available.

HCV Practice Recommendation for IFN-experienced Patients in Asia-Pacific Countries with DAA Available

**Treatment-experienced HCV patients**

- **HCV Genotype 1 or 4 or 6**
  - **Relapser and IL28B CC**
  - **Partial/null responders or IL28B non-CC**

**HCV Genotype 2 or 3**

- **Relapser and non-cirrhotic**
- **Partial/null responders or cirrhosis**

**Cost effectiveness**

- **HCV RNA decline > 1 log**
  - (+)
  - (-)

- **EVR**
  - (+)
  - (-)

- **PegIFN/RBV for 48 weeks**

- **DAA-containing regimens**

- **PegIFN/RBV for 24 weeks**

---

Dot line indicated option of choice, based on cost-effectiveness of available DAA regimens

HCV, hepatitis C virus; DAA, direct acting antivirals; BL, baseline; W, treatment week; IL28B CC, interleukin-28B CC genotype; EVR, early virologic response, HCV RNA decline > 2 logs at week 12; PegIFN, peginterferon; RBV, ribavirin.

WHO HCV Guidelines 2014: Recommendations on HCV Treatment

- All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment (strong recommendation; moderate quality of evidence)

- PegIFN + RBV recommended rather than standard nonpegylated IFN with RBV (strong recommendation; moderate quality of evidence)

- TVR or BOC, in combination with pegIFN/RBV, suggested for GT1 chronic HCV infection rather than pegIFN/RBV alone (conditional recommendation; moderate quality of evidence)

- Sofosbuvir, in combination with RBV with or without pegIFN (depending on HCV genotype), recommended for GT1-4 HCV infection rather than pegIFN/RBV alone (and rather than no treatment for persons who cannot tolerate IFN) (strong recommendation; high quality of evidence)

- Simeprevir, in combination with pegIFN/RBV, recommended for GT1b HCV infection and genotype 1a HCV infection without the Q80K polymorphism, rather than pegIFN/RBV alone (strong recommendation; high quality of evidence)

WHO 2014. Guidelines for the screening, care and treatment of persons with hepatitis C infection
Outline

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The new IFN-free DAAs therapy will become the standard of care for chronic hepatitis C in the Asian Pacific countries in the near future.

However, combination therapy with pegIFN and ribavirin is still the SOC for treatment of CHC in most of Asian countries.

The role of new combination therapies without interferon for chronic hepatitis C needs further elucidation under considering the issue of cost-effectiveness.
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The Asian Pacific Association for the Study of the Liver (APASL)
Taiwan Association for the Study of the Liver (TASL)
The Gastroenterological Society of Taiwan

Welcome to Taiwan
Thank You for Your Attention!