Recent Management of Chronic Hepatitis C

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Meeting today

Cost and future perspectives

- **Guidelines**
  - Recent guidelines of chronic hepatitis C treatment

- **Current management**
  - Peginterferon (Peg-IFN) and ribavirin (RBV)

- **New DAAs**
  - New direct-acting antiviral agents (DAAs)

- **Key studies**
  - Summary of key studies
A Nationwide Seroepidemiology of Hepatitis C Virus Infection in South Korea

Using an estimated 2009 population of Korea, the age, sex and area-adjusted anti-HCV positive rate was 0.78%.
HCV infection, 10% of liver-related mortality (cirrhosis or liver cancers), in a single health care center → about 1,800 deaths/year in Korea
Evolution of Therapy of Chronic Hepatitis C

<table>
<thead>
<tr>
<th>Year</th>
<th>SVR (%)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>≈ 8~12</td>
<td>IFN 6m</td>
</tr>
<tr>
<td>1995</td>
<td>15~20</td>
<td>IFN 12~18m</td>
</tr>
<tr>
<td>1998</td>
<td>38~43</td>
<td>IFN/RBV 6~12m</td>
</tr>
<tr>
<td>2001</td>
<td>25~30</td>
<td>PegIFN 6~12m</td>
</tr>
<tr>
<td>2002</td>
<td>54~56</td>
<td>PegIFN/RBV 6~12m</td>
</tr>
<tr>
<td>2011</td>
<td>67~75</td>
<td>PI + PegIFN/RBV 6~12m</td>
</tr>
<tr>
<td>Near future</td>
<td>≈ 90~100</td>
<td>DAAs</td>
</tr>
</tbody>
</table>
Standard treatment

**Peg-interferon (Peg-IFN) + Ribavirin (RBV)**

- **Peg-IFN-α2b (Peg-intron®, MSD)**
  - 1.5 μg/kg every 1 week (Wt based)

- **Peg-IFN-α2a (Pegasys®, Roche)**
  - 180 μg/kg every 1 week (fixed dose)

**Ribavirin**

- Inhibit viral replication
- Upregulate IFN stimulated genes
- Immunomodulatory effects
- **Dose**: weight-based [15 mg/kg #2 or 1,000 mg (<75 kg), 1200 mg (≥ 75 kg)] PO
  - G1, 4, 5, 6
  - G2,3: obese (BMI>25), insulin resistance, metabolic syndrome, severe fibrosis (LC)
- **800 mg #2 PO (fixed dose)**
  - G2 or G3
Treatment duration using PegIFN+RBV

- **48W**: G1, and G4,5,6
  - G2, G3 + RVR + LVL + No fibrosis

- **24W**: G2, G3
  - G1 + RVR + LVL + No fibrosis

- **16W**: G2, G3 + RVR + LVL + No NPR

- **72W**: G1 + DVR?

RVR, rapid virological response; LVL, low viral load at baseline; LC, liver cirrhosis; NPR, negative predictors of response (cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis); DVR, delayed virological response
# Host and Viral Predictors of SVR

## Host Factors
- **Genetic polymorphism:** IL28B polymorphism
- **Race:** Asian > Caucasian > African
- **Gender:** female
- **Age:** < 40 years
- **Metabolic factors:** normal BMI, no insulin resistance

## Viral Factors
- **Genotype:** 2 or 3
- **Low HCV RNA titer (< 600,000 IU/ml)**

## Histologic Criteria
- Absence of bridging fibrosis or cirrhosis
- Absence of steatosis

## Biochemical Parameters
- Low GGT
- High ALT
- High cholesterol
- Normal Cr
- Normal platelets count

## During Treatment
- Rapid virologic response (RVR)
- Early virologic response (EVR)
- **Adherence to therapy**
- Absence of alcohol abuse
- Supplement of vitamin D, vitamin B12 (?)

Modified from Zakim and Boyer’s Hepatology 6th edition 2012
Outcome of PegIFN+RBV
Large real-world cohort

Baseline factors associated with SVR24 in HCV genotype 1 patients (n=4,520)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic origin:</td>
<td></td>
</tr>
<tr>
<td>Asian vs White</td>
<td>2.04 (1.09–3.80)</td>
</tr>
<tr>
<td>White vs Black</td>
<td>1.93 (1.38–2.69)</td>
</tr>
<tr>
<td>White vs Hispanic</td>
<td>2.56 (1.66–3.95)</td>
</tr>
<tr>
<td>White vs Other</td>
<td>1.03 (0.71–1.49)</td>
</tr>
<tr>
<td>Platelet count:</td>
<td></td>
</tr>
<tr>
<td>≥180 vs &lt;140 x10^9/L</td>
<td>1.96 (1.58–2.43)</td>
</tr>
<tr>
<td>≥140 vs ≥140 to &lt;180 x10^9/L</td>
<td>1.09 (0.92–1.30)</td>
</tr>
<tr>
<td>&gt;3 vs ≤1</td>
<td>1.58 (1.23–2.04)</td>
</tr>
<tr>
<td>&gt;3 vs &gt;1 to 3</td>
<td>1.43 (1.18–1.73)</td>
</tr>
<tr>
<td>ALT ratio:</td>
<td></td>
</tr>
<tr>
<td>HCV RNA per 1-log decrement</td>
<td>1.54 (1.42–1.67)</td>
</tr>
<tr>
<td>Hepatic fibrosis:</td>
<td></td>
</tr>
<tr>
<td>no cirrhosis vs cirrhosis</td>
<td>1.47 (1.24–1.75)</td>
</tr>
<tr>
<td>not assessed/missing vs cirrhosis</td>
<td>1.34 (1.10–1.64)</td>
</tr>
<tr>
<td>AST ratio ≤1.5 vs &gt;1.5</td>
<td>1.42 (1.20–1.69)</td>
</tr>
<tr>
<td>Peginterferon alfa-2a (40KD) vs alfa-2b (12KD)</td>
<td>1.35 (1.02–1.78)</td>
</tr>
<tr>
<td>Age per 10-year decrease</td>
<td>1.15 (1.08–1.22)</td>
</tr>
<tr>
<td>BMI per 1-unit decrease</td>
<td>1.02 (1.01–1.04)</td>
</tr>
<tr>
<td>Hepatic steatosis:</td>
<td></td>
</tr>
<tr>
<td>no vs yes</td>
<td>1.16 (0.98–1.37)</td>
</tr>
<tr>
<td>yes vs not assessed/missing</td>
<td>1.08 (0.91–1.28)</td>
</tr>
</tbody>
</table>

Marcellin P et al. Large real-world PROPHESYS cohort Hepatology 2012
Earlier virological response on treatment increase SVR

Retrospective analysis of Genotype 1 patients (n=453)

<table>
<thead>
<tr>
<th>Time</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 wks  (RVR)</td>
<td>91</td>
</tr>
<tr>
<td>12 wks (cEVR, no RVR)</td>
<td>66</td>
</tr>
<tr>
<td>24 wks (DVR)</td>
<td>45</td>
</tr>
</tbody>
</table>

Ferenci P et al. J Hepatol 2005
SVR in patients with a virologic response by week 4 (RVR) by genotype

Marcellin P et al. Large real-world PROPHESYS cohort Hepatology 2012
Results of treatment in Korea
Retrospective observational study

Retrospective analysis from 14 hospitals in Kyunggi-Incheon areas from 2000 to 2008 (N=758)
M:F=6:4, G1/2/3=61%:36%:2%

Genotype 1
Peg-IFN + RBV 1000 ~ 1200 mg
48 wks

Genotype 2/3
Peg-IFN + RBV 800 mg
24 wks

53.6%

71.4%

Results of treatment

Racial difference in SVR with PegIFN-α2a+RBV

Asian, G1 (n = 324)

RVR 55% 45%
SVR 98% 42%
Overall SVR 76%

Western, IDEAL trial, G1 (n = 1,035)
White 71%, Black 18%, Hispanic 7%, Asians 1~2%

RVR 12% 88%
SVR 80% 36%
Overall SVR 41%

Liu C et al. Antiviral Therapy 2012;17:477
Mc Hutchinson, NEJM 2009;361:580
24-week Treatment in G1 patients with RVR and LVL (< 400,000 IU/mL)

RVR(+) and LVL

- Treated for 24 weeks: 96/27/28
- Treated for 48 weeks: 100/24/24

P = 1.000

RVR(-) or HVL

- Treated for 24 weeks: 44/32/72
- Treated for 48 weeks: 71/55/76

P = 0.001

SVR (%)

RVR, rapid virologic response; LVL, low viral load; HVL, high viral load

Yu et al. HEPATOLOGY 2008;47:1884-1893
In patients with G2 or G3

Results of 16-week treatment according to on-treatment RVR

RVR, rapid virologic response; LVL, low viral load (< 800,000 IU/ml)

<table>
<thead>
<tr>
<th></th>
<th>Treated for 16 weeks</th>
<th>Treated for 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVR(+)</td>
<td>82/28</td>
<td>91/24</td>
</tr>
<tr>
<td>RVR(+) and LVL</td>
<td>88/32</td>
<td>89/55</td>
</tr>
</tbody>
</table>

P = 0.026

Sarrazin, et al. J Hepatol 2010;52:832
Treatment algorithm for patients with genotype 1 chronic HCV infection

*Negative factors for response include advanced liver fibrosis or cirrhosis, obesity, insulin resistance.
Treatment algorithm for patients with genotype 2,3 chronic HCV infection

Week 0
- Peginterferon α + fixed dose ribavirin (800 mg/day)

Week 4
- HCV RNA(-)
  - Negative factors for response*
    - (−)
    - 16 weeks of therapy**
  - Negative factors for response*
    - (+)
    - 24 weeks of therapy

Week 24
- 24 weeks of therapy

*Negative factors for response include advanced liver fibrosis or cirrhosis, obesity, insulin resistance.
Adherence, more important factor than newer therapies

Measures to raise adherence to standard therapy in clinical practice may improve the SVR rates in these patients as effectively as adding protease inhibitors, thus obviating the need for the latter
Reasons for Premature Withdrawal

Park SH et al. Gut Liver 2012
Reasons for Dosage Modifications and Premature Withdrawals from Peginterferon and Ribavirin

<table>
<thead>
<tr>
<th>AE or laboratory abnormality</th>
<th>All Patients (n = 7,163)</th>
<th>Patients without Bridging Fibrosis or Cirrhosis (n = 3,747)</th>
<th>Patients with Bridging Fibrosis or Cirrhosis (n = 1,491)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE or laboratory abnormality</td>
<td>854 (11.9)</td>
<td>427 (11.4)</td>
<td>205 (13.7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>495 (6.9)</td>
<td>283 (7.6)</td>
<td>85 (5.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>219 (3.1)</td>
<td>63 (1.7)</td>
<td>103 (6.9)</td>
</tr>
<tr>
<td>Depression</td>
<td>114 (1.6)</td>
<td>61 (1.6)</td>
<td>19 (1.3)</td>
</tr>
<tr>
<td>AE or laboratory abnormality</td>
<td>556 (7.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>43 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>32 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>73 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>27 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>381 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature withdrawal from ribavirin</td>
<td>97 (1.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Marcellin P et al. Large real-world PROPHESYS cohort Hepatology 2012
### Summary of adverse events

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Category</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-interferon</td>
<td><strong>Flu-like symptoms</strong></td>
<td>Headache, myalgia, fatigue, fever, chill, arthralgia</td>
</tr>
<tr>
<td></td>
<td><strong>Bone marrow suppression</strong></td>
<td>Neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td><strong>Neuropsychiatric symptoms</strong></td>
<td>Depression, irritability, insomnia, apathy</td>
</tr>
<tr>
<td></td>
<td><strong>Autoimmune diseases</strong></td>
<td>Hashimoto thyroiditis (most common), Graves’ disease, systemic lupus erythematosus, Type 1 diabetes, bronchial asthma, pulmonary fibrosis, interstitial pneumonitis, psoriasis, rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td><strong>Gastrointestinal symptoms</strong></td>
<td>Nausea, anorexia, dyspepsia, diarrhea</td>
</tr>
<tr>
<td></td>
<td><strong>Dermatologic complications</strong></td>
<td>Pruritic rash, erythema, induration of injection site, hair loss (alopecia)</td>
</tr>
<tr>
<td></td>
<td><strong>Rare events, but serious complications</strong></td>
<td>Visual impairment due to ischemic retinal diseases (swelling, cotton wool spots, hemorrhage, loss of color vision)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sudden hearing loss or tinnitus</td>
</tr>
<tr>
<td></td>
<td><strong>Others</strong></td>
<td>Respiratory symptoms (cough, shortness of breath)</td>
</tr>
<tr>
<td>Ribavirin</td>
<td><strong>Hematologic</strong></td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td></td>
<td><strong>Psychiatric</strong></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td><strong>Dermatologic</strong></td>
<td>Rash, itching</td>
</tr>
<tr>
<td></td>
<td><strong>Teratogenic</strong></td>
<td>Significant teratogenic effects in animal studies</td>
</tr>
</tbody>
</table>
Summary 1

- Peg-IFN + RBV
  - Standard Tx of chronic HCV infection in Korea
  - HCV is curable. Cure rate is not low in Korea.
  - Earlier virological response (RVR): shortened duration of therapy
  - Target compliance: 80%
    - Optimal management of adverse events

- Adverse events, injection, long duration of therapy
  - Newer treatments are needed
Direct-acting Antiviral Agents (DAAs)

**NS3 serine protease inhibitors**
- Boceprevir, telaprevir (FDA 2011)
- Simeprevir (FDA 2013)
- ABT450/r (in 2014)
- Faldaprevir (in 2014~15)
- Asunaprevir (in 2014~15)

**NS5A inhibitors**
- Daclatasvir (in 2014)
- Ledipasvir (in 2014)
- Ombitasvir (in 2014)

**NS5B polymerase inhibitors**
- Sofosbuvir (FDA 2013)
- Non-nucleoside analogue
- Dasabuvir (ABT-333) (in 2014)

Sofosbuvir + (PEG + RBV)

**NEUTRINO**
- Naïve
- G1, G4, G5, G6

**FISSION**
- Naïve
- G2

**POSITRON**
- PEG ineligible
- G2

**VALENCE**
- All
- G3

**SVR12 (%)**
- SOF+PEG+RBV x 12 Wk
- SOF+RBV x 12 Wk
- SOF+RBV x 24 Wk

**Study Details**

SOF, sofosbuvir (NS5B inhibitor); PEG, peginterferon; RBV, ribavirin; All, both naïve and previously treated patients.
Sofosbuvir + Ledipasvir

SOF, sofosbuvir (NS5B inhibitor); LDV, ledipasvir (NS5A inhibitor)
Simeprevir

SMV, simeprevir (NS3/4A inhibitor); SOF, sofosbuvir (NS5B inhibitor); PEG, peginterferon; RBV, ribavirin; RGT, response-guided therapy

1. Hayashi N et al. J Hepatol 2014 Epub
4. EASL 2014.
Daclatasvir

DCV, daclatasvir (NS5A inhibitor); ASV, asunaprevir (NS3/4A inhibitor); SOF, sofosbuvir (NS5B inhibitor); RBV, ribavirin

* Adding RBV or 24 weeks of therapy did not improve SVR rate.

1. 49th EASL; Apr 9-13, 2014 Abs.
ABT-450/r/Ombitasvir + Dasabuvir ± RBV

ABT, ABT-450 (NS3/4A inhibitor); LC, liver cirrhosis; SOF, sofosbuvir (NS5B inhibitor); PEG, peginterferon; RBV, ribavirin; R, ritonavir; OBT, ombitasvir (NS5A inhibitor); DBV, dasabuvir (NS5B inhibitor)

Recent guidelines — Naïve G1

May, 2014

Recommendation of EASL\(^1\) (E), AASLD\(^2\) (A), or in the near future (F).

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Strongly recommended therapy (I) with high quality of evidence (A)</th>
<th>Duration (weeks)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sofosbuvir + PegIFN + RBV</td>
<td>12</td>
<td>E, A</td>
</tr>
<tr>
<td></td>
<td>Simeprevir (12 Wk) + PegIFN + RBV*</td>
<td>24</td>
<td>E, A</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + Ledipasvir</td>
<td>8~12</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>ABT-450/r/Ombitasvir + Dasabuvir ± RBV</td>
<td>12</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir + Sofosbuvir</td>
<td>12</td>
<td>F</td>
</tr>
<tr>
<td>1b</td>
<td>Daclatasvir + Asunaprevir</td>
<td>24</td>
<td>F</td>
</tr>
</tbody>
</table>

* Not recommended in G1a with Q80K mutation

PegIFN, pegylated interferon alpha; RBV, ribavirin; EASL, European Association for the Study of the Liver; AASLD; American Association for the Study of the Liver

1. EASL. Recommendations on treatment of hepatitis C. http://www.easl.eu/_clinical-practice-guideline
Recent guidelines — Naïve G2 or G3
May, 2014

Recommendation of EASL\(^1\) (E), AASLD\(^2\) (A), or in the near future (F).

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Strongly recommended therapy (I) with high quality of evidence (A)</th>
<th>Duration (weeks)</th>
<th>Ref. (Evidence/recommendation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Sofosbuvir + RBV</td>
<td>12</td>
<td>E, A</td>
</tr>
<tr>
<td>3</td>
<td>Not available</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + RBV</td>
<td>24</td>
<td>E(A2), A(B-I)</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + PegIFN + RBV</td>
<td>12</td>
<td>E(A2), A(A-IIa)</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + Daclatasvir</td>
<td>12</td>
<td>E(B1)</td>
</tr>
</tbody>
</table>

1. EASL. Recommendations on treatment of hepatitis C. http://www.easl.eu/_clinical-practice-guideline
In the future

• One pill one day
  – Irrespective of genotype (no need of genotyping)
  – Shorter treatment course (2~3 months)
  – Fewer adverse events (no need of specialists)
The Problem is Cost

- **Sovaldi® (Sofosbuvir)** 400 mg x 84 days: $84,000
- **Pegasys® (Peg-IFN-a2)** 180 ug x 24 weeks: $19,600
- **Barclude® (Entecavir)** 0.5mg x 365 days: $14,200
- **Lanston® (Lansoprazole)** 30 mg x 365 days: $720

Current price in USA, Calculated from http://www.rxpricequotes.com/
Lessons from HIV treatment
Summary-2

- All oral regimens, a standard treatment in the near future
  - Sofosbuvir/Ledipasvir
  - ABT-450/r/Ombitasvir + Dasabuvir
  - Daclatasvir

- Coexistence of DAAs and PegIFN/RBV
  - (Simeprevir / Sofosbuvir / Daclatasvir) + PegIFN + RBV

- Efforts to reduce the high cost!
Thank you for your attention

Recent Mx of Chronic Hepatitis C

Jae-Jun Shim, M.D.
Kyung Hee University Hospital
The Liver Week 2014