Management of HBV-HCV Co-infection:

Resolved and Unresolved Issues

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Toward Elimination and Eradication of Viral Hepatitis B and C

-HBV vaccination program-
-Active treatment of HBV and HCV-

Chen DS. Fighting against viral hepatitis: Lessons from Taiwan
Hepatology 2011;54:381
Effects of Hepatitis B Vaccination on HBV-Related Diseases

• Acute / Fulminant Hepatitis
• Chronic Hepatitis
• Hepatocellular Carcinoma

* The First World Universal Hepatitis B Vaccination Program Was Launched in July 1984 in Taiwan
Chronicles for CHB/CHC Reimbursement Policies in Taiwan - Bureau of National Health Insurance (BNHI) -

- Oct. 2003
  - CHB: LAM (18 months), IFN (24 weeks).
  - CHC: IFN plus ribavirin (24 weeks)

- Oct. 2005:
  - CHB: Adefovir monotherapy for LAM-R rescue therapy
  - CHB: Peginterferon alfa-2a

- Oct. 2008:
  - CHB: Entecavir

- Nov. 2009:
  - CHB: NUCs for 3 years
  - CHC: Pegylated Interferon and ribavirin by RGT

- Jul. 2010:
  - CHB: Liver cirrhosis with HBV DNA >2000 IU/mL, long-term therapy
  - 2011: Tenofovir
In total, around 100,000 CHB and 60,000 CHC cases treated in the last ten years.

### Treated CHB/CHC cases by NHI Program in Taiwan:

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>3,186</td>
<td>6,416</td>
<td>6,309</td>
<td>6,229</td>
<td>6,669</td>
<td>7,947</td>
<td>11,031</td>
<td>21,023</td>
<td>18,713</td>
<td>13,855</td>
</tr>
<tr>
<td>HCV</td>
<td>1,490</td>
<td>3,738</td>
<td>3,575</td>
<td>3,147</td>
<td>3,917</td>
<td>3,592</td>
<td>5,560</td>
<td>12,248</td>
<td>10,597</td>
<td>7,706</td>
</tr>
<tr>
<td>HBV (Resistant)</td>
<td>0</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>941</td>
<td>1,722</td>
<td>1,246</td>
<td>1,206</td>
<td>1,207</td>
<td>900</td>
<td>569</td>
</tr>
<tr>
<td>HBV (re-treated)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt;3</td>
<td>140</td>
<td>616</td>
<td>1,517</td>
<td>2,006</td>
<td>1,230</td>
<td>1,217</td>
</tr>
<tr>
<td>HCV(re-treated)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>339</td>
<td>1,053</td>
<td>873</td>
<td>706</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt;3</td>
<td>251</td>
<td>152</td>
<td>125</td>
</tr>
</tbody>
</table>
The declining order of CLD and LC ranking among the ten leading causes of death in Taiwan

![Graph showing the declining order of CLD and LC ranking among the ten leading causes of death in Taiwan. The x-axis represents the years from 2001 to 2012, and the y-axis represents the ranking from 5th to 10th. The graph shows that CLD and LC have moved from 5th to 10th over these years.]
HBV and HCV co-infection: A forgotten population

Outline

• Dual chronic HCV/HBV infection
  – Epidemiology
  – Clinical significance

• Strategy to manage patients with dual HCV/HBV

• Using peg-IFN/RBV therapy to treat patients with dual HCV/HBV and active HCV infection
  – Short-term serologic and virologic responses
  – Long-term impact on clinical outcomes

• Unresolved issues

• Conclusions
Outline

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  – Clinical significance
• Strategy to manage patients with dual HCV/HBV
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  – Long-term impact on clinical outcomes
• Unresolved issues
• Conclusions
Estimated prevalence of HBV–HCV co-infection in South-East Asia

- Worldwide, 350–400 million people worldwide with chronic HBV and an estimated 130–210 million people have chronic HCV\(^1,2\)
  - HBV–HCV co-infection is prevalent in areas where HBV is endemic, such as South-East Asia\(^3\)

HBV–HCV co-infection is frequently found in high-risk populations

Long-term outcomes:
Acute HCV superinfection vs. active CHB
(Hospital-based, case control study)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>HCV on HBV</th>
<th>HBV alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>20 (31.3%)</td>
<td>11 (17.2%)</td>
</tr>
<tr>
<td>HCC</td>
<td>6 (9.4%)</td>
<td>3 (4.7%)</td>
</tr>
</tbody>
</table>

Liaw YF et al, Gastroenterology 2004
HBV–HCV co-infected patients are at increased risk of HCC: a community-based cohort

HCC risk is significantly higher in HBV–HCV co-infected patients than in those with mono infection ($P = 0.030$ and 0.0019, respectively).

<table>
<thead>
<tr>
<th></th>
<th>HBsAg-ve Anti-HCV-ve</th>
<th>HBsAg+ve Anti-HCV-ve</th>
<th>HBsAg-ve Anti-HCV+ve</th>
<th>HBsAg+ve Anti-HCV+ve</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td>22.35 (16.05–31.13)</td>
<td>164.98 (122.36–222.46)</td>
<td>492.62 (372.31–651.79)</td>
<td>875.28 (518.38–1,477.90)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>40.26 (31.12–52.07)</td>
<td>593.31 (518.58–678.80)</td>
<td>683.99 (513.91–910.36)</td>
<td>1,130.75 (721.25–1,772.76)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

HCC = hepatocellular carcinoma; HBsAg = hepatitis B surface antigen.

A ten-year follow-up of patients with dual chronic hepatitis B and C: Outcomes and determinants

<table>
<thead>
<tr>
<th></th>
<th>HBV Monoinfection</th>
<th>HBV/HCV coinfection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of patients</td>
<td>No. (%) of patients</td>
</tr>
<tr>
<td>Number of case</td>
<td>111</td>
<td>111</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>48 (43.2)</td>
<td>48 (43.2)</td>
</tr>
<tr>
<td>Male</td>
<td>63 (56.8)</td>
<td>63 (56.8)</td>
</tr>
<tr>
<td>Age Mean±SD (range)</td>
<td>48.0±12.0 (27.5,75.8)</td>
<td>47.9±12.3 (20.6,75.8)</td>
</tr>
<tr>
<td>Serum ALT level (U/L) Mean±SD (range)</td>
<td>27.5±32.8 (5,281)</td>
<td>109.9±158.0 (12,960)</td>
</tr>
<tr>
<td>Serum Log10 HBV DNA level (IU/mL) Mean±SD (range)</td>
<td>2.5±1.5 (1.2,8.6)</td>
<td>2.7±1.2 (0.3,8.1)</td>
</tr>
<tr>
<td>HBsAg level (IU/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100</td>
<td>44 (39.6)</td>
<td>43 (38.7)</td>
</tr>
<tr>
<td>101-1,000</td>
<td>31 (27.9)</td>
<td>32 (28.8)</td>
</tr>
<tr>
<td>1,001-10,000</td>
<td>33 (29.7)</td>
<td>33 (29.7)</td>
</tr>
<tr>
<td>&gt;10,000</td>
<td>3 (2.7)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>1491.4</td>
<td>1068.8</td>
</tr>
<tr>
<td>Patient-years of follow-up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Liu CJ et al (AASLD 2014)
Cumulative incidence of HBsAg seroclearance, HCC and cirrhosis in cases with HBV/HCV co-infection and matched controls with HBV mono-infection

<table>
<thead>
<tr>
<th></th>
<th>HBV and HCV co-infection (N=111)</th>
<th>HBV mono-infection (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBsAg seroclearance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-years of follow-up</td>
<td>1174.55</td>
<td>1557.37</td>
</tr>
<tr>
<td>No of case</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Incidence rate per 100 P-ys (95% CI)</td>
<td>1.70 (1.10-2.64)</td>
<td>1.35 (0.88-2.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>HCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-years of follow-up</td>
<td>1255.78</td>
<td>1703.65</td>
</tr>
<tr>
<td>No of case</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Incidence rate per 100 P-ys (95% CI)</td>
<td>1.51 (0.97-2.37)</td>
<td>0.47 (0.23-0.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-years of follow-up</td>
<td>1137.91</td>
<td>1599.00</td>
</tr>
<tr>
<td>No of case</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>Incidence rate per 100 P-ys (95% CI)</td>
<td>2.72 (1.92-3.87)</td>
<td>1.00 (0.61-1.63)</td>
</tr>
</tbody>
</table>
Outcomes of HBV/HCV versus HBV (1): Adjusted for HBV DNA, HBsAg and ALT

Liu CJ et al (AASLD 2014)
Outcomes of HBV/HCV versus HBV (2): Adjusted for HBV DNA, HBsAg and ALT

Liu CJ et al (AASLD 2014)
Outline

• Dual chronic HCV/HBV infection
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• Unresolved issues

• Conclusions
Treatment of Dual Infection

Ideal target: Both viruses

*Alternative strategy, targeting*

Dominant one for hepatitis activity

One most easily be treated
Profiles of HCV and HBV in Patients with Dual Infection

- Active HCV / Inactive HBV: 48%
- Active HCV / Active HBV: 23%
- Inactive HCV / Active HBV: 14.5%
- Inactive HCV / Inactive HBV: 14.5%

Raimondo G et al, Hepatology 2006
Viral Phenotype of Dual HCV/HBV (NTUH, n=139)

Liu CJ et al, (unpublished)
HCV/HBV Dual Infection

• HCV is the priority target
• Practical goals for treatment
  – Eradicate HCV
  – Control HBV (ideally to eradicate)
Peg-IFNα-2a + ribavirin in patients with HCV/HBV or HCV alone: study design


*1000 mg/day if body weight < 75 kg; 1200 mg/day if body weight ≥ 75 kg.
Peg-IFN = pegylated interferon; RBV = ribavirin.
Similar SVR rates in Asian HBV–HCV co-infected and HCV mono-infected patients


Intention-to-treat population.
SVR = sustained virological response.
Peginterferon alfa-2a + ribavirin in patients with HCV/HBV or HCV alone – Follow-up

HCV-infected patients (N=160)

- HCV GT1
  - PEGASYS (180 µg/week)+ RBV (1000–1200 mg/day)* (N=110)

- HCV GT 2 or 3
  - PEGASYS (180 µg/week)+ RBV (800 mg/day) (N=50)

Coinfected HCV/HBV patients (N=161)

- HCV GT 1/HBV
  - PEGASYS (180 µg/week)+ RBV (1000–1200 mg/day)* (N=97)

- HCV GT 2 or 3/HBV
  - PEGASYS (180 µg/week)+ RBV (800 mg/day) (N=64)

5-year post-treatment FU:
-HCV SVR (long-term)

*1000 mg/day if body weight <75 kg
1200 mg/day if body weight ≥75 kg

Liu CJ et al, EASL 2012
Yu ML, et al. Hepatology
HCV SVR is durable in HCV mono-infected patients as well as HBV–HCV co-infected patients

Intention-to-treat population.
SVR = sustained virological response.

### HBsAg clearance at end-of-treatment and at 6 months post-Peg-IFN/RBV

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>HCV genotype 1 /HBV</th>
<th>HCV genotype 2/3 /HBV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-of-treatment</strong></td>
<td>19/161 (11.8%)</td>
<td>14/97 (14.4%)</td>
<td>5/64 (7.8%)</td>
<td>0.203</td>
</tr>
<tr>
<td><strong>Follow-up at 6 months</strong></td>
<td>18/161 (11.2%)</td>
<td>12/97 (12.4%)</td>
<td>6/64 (9.4%)</td>
<td>0.555</td>
</tr>
</tbody>
</table>

Seroconversion to anti-HBs noted in 8 of the 18 cases (44.4%) at 6 months follow-up

Around 30% of patients have cleared HBsAg 5 years after treatment with Peg-IFN alfa-2a/RBV

Curative option of serum HBsAg level ≤ 20 IU/mL at baseline for HBsAg clearance 6 months post-treatment

Baseline HBsAg level predicts HBsAg clearance at 6 months post-treatment

Cut-off of serum HBsAg level ≤ 20 IU/mL at baseline for HBsAg clearance 6 months post-treatment

<table>
<thead>
<tr>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>91.2%</td>
<td>85.7%</td>
<td>84%</td>
<td>41.4%</td>
<td>97.8%</td>
</tr>
</tbody>
</table>

The HBsAg clearance rate among the 30 patients with baseline serum HBsAg ≤ 20 IU/mL (40%, n = 12) was significantly greater than among the 90 patients with baseline serum HBsAg >20 IU/mL (2.2%, n=2; P <0.05)

NPV = negative predictive value; PPV = positive predictive value.

Characteristics of 9 patients developing HCC post-trial follow-up

• At baseline
  – 8 (88.9%) pts had dual HCV/HBV, 1 (11.1%) had mono-HCV
  – 5 (55.6%) had cirrhosis, 3 (33.3%) had stage 2 fibrosis, and 1 (11.1%) had stage 1 fibrosis

• After treatment
  – 7 obtained HCV SVR-LTFU, 7 had biochemical remission and 3 developed seroclearance of HBsAg

• Median (range) of time from end of treatment to diagnosis of HCC: 3 yrs (1~5 yrs)

Yu ML et al. Hepatology 2013
**Anti-HCV treatment reduces co-infected patients’ risk of HCC and improves survival**

A population-based, retrospective cohort study examined the risk of HCC, mortality and adverse events in 1,096 treated and 18,988 untreated HCV–HBV co-infected patients.

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>Liver-related mortality</th>
<th>Incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Peg-IFNα + RBV</td>
<td>0.42</td>
<td>(0.34–0.52)</td>
</tr>
</tbody>
</table>

Compared with untreated patients, patients on anti-HCV combination treatment (Peg-IFNα + RBV) have significantly reduced incidences of all-cause mortality, liver-related mortality and HCC.

CI = confidence interval; HR = hazard ratio

Resolved issues about treatment

• Short-term outcomes achieved
  – HCV SVR achieved
  – HBV DNA remains undetectable
  – HBsAg cleared

• Long-term outcomes improved
  – Overall survival
  – Liver-related mortality
  – Development of HCC
Current management guidelines for HBV–HCV co-infection

• It is helpful to determine which virus is dominant in co-infected patients before treatment$^1$
  – HBV DNA levels are often low or undetectable and HCV is usually responsible for the activity of chronic hepatitis in most patients$^{2,3}$

• In HBV–HCV co-infected patients who are HCV-viremic, antiviral treatment may be selected using the same criteria as for those patients with HCV mono-infection$^{1–3}$

Proposed algorithm for management of HCV and HBV co-infection

HBsAg-positive & anti-HCV-positive

Active HCV / Inactive HBV
- Treat HCV: P+R or DAA-based
- Observe HBV reactivation

Active HCV / Active HBV
- Treat HCV: P+R or DAA-based
- Observe HBV response & reactivation
  - Or
  - Treat HCV & HBV: P+R+NUC

Active HBV / Inactive HCV
- Treat HBV: P or NUC

Inactive HCV / Inactive HBV
- Observation

P: Peg-IFN α
R: ribavirin
NUC: nucleos(t)ide analogue
DAA: Direct acting antiviral (HCV)

Liu CJ. J Gastroenterol Hepatol 2014
Liu CJ and Chen PJ. World J Gastroenterol 2014
Unresolved issues

• Prevention and management of HBV reactivation
• Host and viral factors affecting natural and treatment outcomes of patients with dual chronic HCV/HBV
  – Host: miR-122, IL28B genotype
  – Viral: HCV ISDR, HBV precore/BCP polymorphisms
• Optimal strategies to treat patients with dual HCV/HBV and active HBV infection
• Role of new DAA-based therapy
• Outcomes and mechanisms of occult hepatitis B (OBI) in patients who developed HBsAg seroclearance post-treatment
Relationship of baseline miR-122 level and HBsAg level change in HBV/HCV dually infected patients receiving Peg-IFN/RBV therapy

Cheng HR et al. Hepatol Int (online)
Mechanism of undetectable HBsAg in patients developing occult HBV post-treatment

<table>
<thead>
<tr>
<th>HBV region</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhancer/core promoter:</td>
<td>Grl-2 (A1762T (xK130M))</td>
<td>Grl-4 (C1715G(xT113E))</td>
<td>Grl-8 (A1762T(xK130M))</td>
</tr>
<tr>
<td>Nucleotides 1625-1775</td>
<td>A1764A(xV131I)</td>
<td>A1762T(xK130M)</td>
<td>G1764A(xV131I)</td>
</tr>
<tr>
<td>S2 promoter: nucleotide 2960-3180</td>
<td>C1773T(xV132V)</td>
<td>C1715G(xT113E)</td>
<td>C1764A(xV131I)</td>
</tr>
<tr>
<td></td>
<td>C3050T(preS1T68I)</td>
<td>G1764A(xV131I)</td>
<td>C1764A(xV131I)</td>
</tr>
<tr>
<td></td>
<td>C3109A(preSIV88M)</td>
<td>C1715G(xT113E)</td>
<td>C1764A(xV131I)</td>
</tr>
<tr>
<td></td>
<td>G3157A(preSIV104K)</td>
<td>C1715G(xT113E)</td>
<td>C1764A(xV131I)</td>
</tr>
<tr>
<td></td>
<td>C3050T(preSIT68I)</td>
<td>G1764A(xV131I)</td>
<td>C1764A(xV131I)</td>
</tr>
<tr>
<td>Cytotoxic T lymphocyte:</td>
<td>G285A (sG44E)</td>
<td>C287G (sT45A)</td>
<td>G285A (sG44E)</td>
</tr>
<tr>
<td><em>a</em> determinant: amino acid 124-147(S gene)</td>
<td>G293A/T294C/</td>
<td>C248G (sL32V)</td>
<td>G285A (sG44E)</td>
</tr>
<tr>
<td>Overlapping polymerase gene:</td>
<td>T531C(sI126T)</td>
<td>G295T (sV47T)</td>
<td>C287G (sT45A)</td>
</tr>
<tr>
<td>amino acid 36-156</td>
<td>T581A(sI143T)</td>
<td>T300C (sL49P)</td>
<td>G293A/T294C/</td>
</tr>
<tr>
<td></td>
<td>G295T (rtV56L)</td>
<td>T265A (sF41Y)</td>
<td>G295T (sV47T)</td>
</tr>
<tr>
<td></td>
<td>T491A(rtI121N)</td>
<td>C248G (sL32V)</td>
<td>G295T (rtV56L)</td>
</tr>
<tr>
<td></td>
<td>T344A(rtL72Q)</td>
<td>C248G (sL32V)</td>
<td>G295T (rtV56L)</td>
</tr>
</tbody>
</table>

**Finding:** One mutation, C3050T (preS1T68I), decreased S promoter activity, possibly contributing to HBsAg undetectability.

Prevalence of OBI: 40%

-The effect of C3050T mutation on S promoter activity by reporter assay. Huh-7 cells were transfected with pSP-Luc or pSP-Luc-M (carrying the C3050T mutation).

-The cell lysates were prepared for assessment of luciferase activity.

Cheng HR et al. Liver Int (online)
Summary

• HBV–HCV co-infection is prevalent in some parts of South-East Asia
  – HBV endemic countries
  – High risk populations include IVDUs and HIV patients
• HBV–HCV co-infected patients should be treated with the same criteria as mono-infected HCV patients
  – HCV SVR rates in HBV–HCV co-infected patients are similar to those with HCV mono-infection
• Peg-IFN/RBV therapy may also result in HBV responses
  – Clearance of HBsAg is possible in a significant proportion
• Anti-HCV treatment may improve long-term outcomes
  – Post-treatment follow-up is still recommended
Thank you for your attention