Management of Chronic Hepatitis B:
Why we care and how to treat?

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Myanmar
I have no financial relationships to disclose relevant to my presentation.
Where is Myanmar?

About Myanmar
(Formerly called Burma)
Shwedagon pagoda
Hepatitis B; Why do we care?

- Because HBV is the main causal factor of HCC
- Direct correlation between HBV viral load and HCC
- Treatment of HBV can prevent HCC

What are the evidences?
HBV is the main causal factor of HCC

What are the Evidences?
HBV and HCC

- Chronic HBV was noted to be associated with the development of HCC.


- Chronic hepatitis B virus has been linked epidemiologically to the development of HCC for more than 30 years.
  - Epidemiological evidence
  - Evidence by reduction of HBV incidence by HB vaccination
  - Correlation between HBV viral load and HCC

Geographical correlation between the global incidences of HBV carrier state (a) and hepatocellular carcinoma (b).

The incidence of HCC is directly related to the prevalence of chronic infections caused by HBV.

(Ref: Lai & Locanini, Hepatitis B Virus, International Medical Press Ltd, 2002)
Correlation between HBV viral load and HCC

What are the Evidences?
Risk of HCC and Cirrhosis According to Baseline HBV DNA

Viral Load Associated with Risk of HCC

Cumulative incidence of HCC by baseline HBV DNA

Adjusted for gender, age, anti-HCV, habits of cigarette smoking and alcohol consumption.

Chen et al. 14th APASL. 2004. Poster
Persistent presence of HBeAg and persistently high serum HBV DNA levels are associated with increased risk of cirrhosis and HCC.

Treatment of HBV can prevent HCC

What are the Evidences?
Treatment of HBV can prevent HCC

- Antiviral therapy
  - effective in causing prolonged lowering of serum levels of HBV DNA.

- Prolonged antiviral therapy
  - may reduce the risk of HCC among certain patients with chronic hepatitis B.
Evidence to support the notion that antiviral therapy can prevent HCC

- Prevention of HBV-related HCC with
  - Interferon
  - Nucleos/tide Analogue
Interferon Treatment

• 233 IFN–treated vs. 233 matched controls

NB: HCC was reduced significantly only in patients with pre-existing cirrhosis (3/19 IFN vs 14/24 controls; p<0.01)

Lin et al, J Hepatol 2007; 40:45-52
Forest plot to compare interferon with placebo or no treatment in the development of HCC.

*Sung et al., Aliment Pharmacol Ther*  
*2008; 28:1067-77*
Prevention of HCC by Nucleos/tide Therapy

Forest plot to compare interferon with placebo or no treatment in the development of HCC.

Sung et al., Aliment Pharmacol Ther 2008;28:1067-77
Conclusions

• Successful treatment of CHB can decrease the incidence of HCC.

• Nucleos/tide analogues probably more effective than IFN
Treatment of Chronic Hepatitis B

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Today’s Topics

• Goal of Therapy
• 4 Phases of Chronic HBV Infection
• When To Treat?
• Beyond the Guidelines: Treatment of Normal ALT Patients
• How to treat? With what drug?
• NAs When to stop?
• Combination Therapy
• HBsAg Quantification
• Newer Antiviral Therapy
• Summary: What is new in 2013?
Goal of Therapy

- To improve quality of life and survival by preventing progression of the disease to
  - Cirrhosis
  - Decompensated cirrhosis
  - End-stage liver disease (ESLD)
  - HCC
  - Death

- This goal can be achieved
  - If HBV replication can be suppressed in a sustained manner

(EASL CPGs: Management of chronic hepatitis B; J Hepatol 2009;50:227-42)
## Current Understanding of HBV Infection

### 4 Phases of Chronic HBV Infection

<table>
<thead>
<tr>
<th>Phase</th>
<th>Immune Tolerant</th>
<th>Immune Clearance</th>
<th>Inactive Carrier State</th>
<th>Reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Minimal inflammation and fibrosis</td>
<td>Chronic active inflammation</td>
<td>Mild hepatitis and minimal fibrosis</td>
<td>Active inflammation</td>
</tr>
</tbody>
</table>

**Optimal treatment times**

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**Graham R. Foster. Clinical dilemmas in viral liver disease, 2010**
When To Treat?

• **Traditional concept**
  – ALT based \(< 2 \text{ULN} \rightarrow \text{no Tx}\)
  – Biopsy based \(< 3 \text{ HAI score (Ishak)} \rightarrow \text{no Tx}\)
  – Not to treat if in immune-tolerant phase

• **Current and Controversial concept**
  – High viral load irrespective of ALT level
  – To treat even if in immune-tolerant phase
Guidelines for Starting Treatment

- **APASL (2012)**
  - HBeAg positive
    - ALT > 2 ULN and HBV DNA > 20000 IU/mL
  - HBeAg negative
    - ALT > 2 ULN and HBV DNA > 2000 IU/mL
  - Advanced fibrosis or CL with any ALT level

- **EASL (2012)**
  - ALT > 2 ULN and HBV DNA > 2000 IU/mL
  - ALT normal or high end
    - moderate to severe fibrosis even if ALT is normal.
    - Age, health status, family history of HCC or CL are also considered

*APASL, 2012 Update
EASL, Journal of Hepatology 2012, 57: 167-185*
Beyond the Guidelines: Treatment of Normal ALT Patients
Antiviral Therapy in HBeAg (+) patients with ALT < 2x ULN

CON

- Belief that there’s no disease progression, minimal histological lesions
- Immune tolerance – low probability of anti-HBe seroconversion
- (PEG-) IFN α: not effective
- NAs: inhibition of HBV replication
  - Probably life-long therapy in young patients: long-term safety, patient reluctance, family planning?

Zouim F. Mason WS. Gut 2012, 61 333-336,
EASL Clinical Practice Guidelines Management of Chronic Hepatitis B
Virus Infection J Hepatol 2012, 57: 167-185
(PEG-)IFNα (pegylated) - interferon alpha: NA: nucleos (t)ide analogue, HBV hepatitis B virus
Antiviral Therapy in HBeAg (+) patients with ALT < 2x ULN

**PRO**

- Maintenance of high HBV replication – increasing number of infected hepatocytes
- High risk of HBV transmission
- Patients with high HBV DNA levels are at risk of HCC regardless of ALT level


(PEG-)IFNa (pegylated)- interferon alpha: NA: uncleos (t)ide analogue, HBV hepatitis Bvirus
Clinical dilemma

Should we treat immune tolerant patients to prevent HCC?
What is immune tolerance?

- Maternal HBeAg induces tolerance in neonate immune system to HBsAg and HBeAg
- Hepatitis B specific T cells are hyporesponsive
- Ineffective antigen processing
- Anergy, deletion, altered maturation of virus specific effector cells and expansion of regulatory T cells

Carey I et al J Virol 2011;85:2416
Viral Load Associated with Risk of HCC

Cumulative incidence of HCC by baseline HBV DNA

Adjusted for gender, age, anti-HCV, habits of cigarette smoking and alcohol consumption.

Chen et al. 14th APASL. 2004. Poster
Immune Tolerance and HCC

• Viral replication in immune tolerant expected to be very high $10^9$-$10^{10}$

• Clonal hepatocyte repopulation: higher risk of HCC$^4$

1 Wang HY, J Virol 2010;84: 3454-63
2 Carey I et al J Virol 2011;85:2416
3 Xu C Virology 2007;359:283e94.
Hypothesis: clonal hepatocyte repopulation

Chronic hepatocellular injury and/or impaired regeneration

Emergence of phenotypically altered cells resistant to cytotoxicity and/or to growth arrest

Selective clonal growth and development of dysplasia with altered growth pattern

Tx of Normal ALT Patients

• Two pediatric studies
  – Sequential therapy with LAM → IFN
  – HBsAg loss/seroconversion 17-21%

• LAM reduction in viral levels allowed
  – HBV specific cell mediated immunity,
  – reversal of hyporesponsiveness
  – sets platform for immune response to IFN

Carey I et al JOURNAL OF VIROLOGY, Mar. 2011, p. 2416-2428
Poddar U et al Journal of Viral Hepatitis, 2013, 20, 311-316
How to treat?
With what drugs?
Drugs available

- Immunomodulators
  - Interferons
  - Pegylated Interferon
- Nucleoside/tide analogues (NA)
  - Lamivudine
  - Adefovir
  - Entecavir
  - Tenofovir
Interferons

- Injection Pegylated Interferon
  - IFN α2a
    - Injection Pegasys (Roche)
      - 180 μg fixed dose
    - The only IFN approved by US FDA for the Tx of CHB
  - IFN α2b
    - Injection PegIntron (MSD)
      - Weight based
      - BW in kg x 1.5 = dosage
      - 50 μg, 80 μg, 100 μg
Available Nucleoside/tide Analogues

- Lamivudine
- Adefovir
- Entecavir
- Tenofovir

Nucleoside

Nitrogen-containing ring structures attached to a sugar.

Nucleotide

Addition of a phosphate produces a nucleotide.

Nucleoside and Nucleotide diagrams with molecular structures.
HBV Treatment Goals

Sustained Remission

PEG-IFN

Low viremia

ALT normalization

Immune control, no further need to continue the drug

Maintained Remission

NA

Low viremia

ALT normalization

No immune control, continued need for antiviral drugs
Can treatment with NA be stopped?

New cells

Nucleoside analogs

Nucleoside analogs

HBV mRNA

DNA dependent polymerase

DNA dependent polymerase

CCC DNA

CCC DNA

HBV mRNA

RNA dependent polymerase

RNA dependent polymerase

Golgi

ER
Can therapy with NAs be stopped?

- Long-term viral suppression
- Off-therapy response
  - unclear – limited sustained immune control
- ‘When can therapy be stopped?’
- Monitoring qHBsAg may help us identify patients who can stop NAs with a low chance of relapse
When to stop?
**Current guidelines about NA cessation**

**Current suggestions**

<table>
<thead>
<tr>
<th></th>
<th>AASLD 2009(^1)</th>
<th>APASL 2012(^2)</th>
<th>EASL 2012(^3)</th>
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</thead>
<tbody>
<tr>
<td>HBeAg-positive patients</td>
<td>6 months HBeAg seroconversion &amp; undetectable HBV DNA</td>
<td>6 month HBeAg seroconversion &amp; undetectable HBV DNA</td>
<td>12 months HBeAg seroconversion &amp; undetectable HBV DNA</td>
</tr>
<tr>
<td>HBeAg-negative patients</td>
<td>HBsAg seroclearance</td>
<td>12 months undetectable HBV DNA</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^1\)Lok, *Hepatology* 2009; \(^2\)Liaw APASL 2012, \(^3\)EASL, *J Hepatol* 2012
Can therapy with analogues be stopped?

• HBeAg (+)
  – After HBe sero-conversion
  – After 6 months of additional therapy
  – In non cirrhotic

• HBeAg (-)
  – Never
  – HBs seroconversion nearly never happens

• COL
  – Never
Long-term NA Treatment
Conclusions

• Good virological response
  • potent last generation NA with high genetic barrier
• Profound improvement in inflammation & fibrosis score
• Reduction of liver failure and most probably also of HCC and all cause mortality
• NA therapy cannot be stopped in vast majority of patients
Combination therapy
The future for HBV treatment: combination of a potent NA and PEG-IFN
On-therapy HBV DNA Suppression and End of Follow-up Responses

Mean HBV DNA (log_{10} copies/ml)

On-treatment

Follow-up

PEG-IFN
HBeAg seroconversion at EOF = 32%

Lamivudine
HBeAg seroconversion at EOF = 19%

PEG-IFN + lamivudine
HBeAg seroconversion at EOF = 27%

*all numbers shown are log_{10} reduction from baseline

Combination Therapy

• Two pediatric studies
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• LAM reduction in viral levels allowed
  – HBV specific cell mediated immunity,
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  – sets platform for immune response to IFN

Carey I et al JOURNAL OF VIROLOGY, Mar. 2011, p. 2416-2428
Poddar U et al Journal of Viral Hepatitis, 2013, 20, 311-316
Coming back to immune modulation...

NIDDK HBRN:
- PEG IFN 40 wks
- ETV 48 wks

48 wks

Tenofovir +/- PEG IFN

Weeks

Weeks

48

72

120

PEG

TDF

PEG 16 wks

TDF

PEG
ETV and PEG-IFN (ARES Study)

- HBe Ag positive study
- Multicenter, open-label, randomized controlled trial

**Responses?**

- **Entecavir 0.5mg daily**
- **Follow-up**

Response: combined presence of HBeAg loss and HBV DNA level <200 IU/ml at week 48

*Sonneveld et al. AASLD 2012*
ETV and PEG-IFN (ARES Study)
Virological outcomes at week 48

Sonneveld et al. AASLD 2012
New On-treatment Monitoring Test: HBsAg Quantification
HBsAg loss = cccDNA very low

- 29 biopsies: HBsAg loss
- HBV DNA(+): 100%(1,68 cop/cell)
- ccc DNA(+): 79%(0.03 cop/cell)

Yuen et al., Gastroenterology 2008
HBsAg quantification: technics

**Architect platform**
- Anti-HBsAb
- Acridinium

(<0.05-250 UI/ml
Dilution manuelle 1/120 ou 1/500)

0.05 UI/ml HBsAg

**Elecsys HBsAg II**
- Anti-HBsAb
- Biotine
- Streptavidin
- Ruthenium

(<0.05-52 000 UI/ml
dilution automatique 1/100 ou 1/400)

4000 viral particules /ml
Different meanings of HBV DNA and HBsAg in CHB

<table>
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<tr>
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<th>HBV DNA</th>
<th>HBsAg</th>
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<tbody>
<tr>
<td><strong>Virology</strong></td>
<td>Dane particle</td>
<td>Dane particle and subviral particles</td>
</tr>
<tr>
<td><strong>Natural history</strong></td>
<td>Reduced after HBeAg seroconversion but relapse on immune escape</td>
<td>Very slow reduction over time regardless of HBV DNA levels or disease activity</td>
</tr>
<tr>
<td><strong>Implication</strong></td>
<td>Viral replication</td>
<td>Immune clearance of infected hepatocytes</td>
</tr>
</tbody>
</table>
HBs Ag quantification

PegIFN-α2a, HBeAg-negative

Treatment

Moucan R et al., Hepatology 2009, 49 1151-7
HBsAg kinetics
Tenofovir

Reduction of HBsAg (Log IU/mL)

Weeks

12 24 36 48 64 80 96 108 120 132 144

0.00
-1.00
-2.00
-3.00
-4.00
-5.00
-6.00

No HBsAg loss

HBsAg loss

Newer Antiviral Therapies
Targeting Different Stages in the HBV Lifecycle

**Innate responses**

**Block Entry**

**Target cccDNA**

**DNA dependent polymerase**

**Target HBV mRNA**

**HBV mRNA**

**Target Packaging**

**Target HBV DNA**

**Assembly/Export**

**HBV DNA Replication**

**RNA dependent polymerase**

**ER**

**Golgi**

**Immune Activation**

**Adaptive Immune Response**
Summary: What is new in 2013?

• Lower threshold for determining transition to immune active phase or newer indications for HBV Tx
  – HBV DNA (slightly lower?)
  – ALT levels (slightly higher?)
  – Histologic evidence of inflammation (a little?)
  – “Old” young adult
• Combination therapy
• HBsAg quantification (qHBsAg) for on-treatment monitoring for the prediction of cure.
• Newer antivirals
Thank You