Viral hepatitis Prevention Board

Clinical aspects of hepatitis B
Natural History and serological markers acute and chronic hepatitis B

Acute hepatitis B

- Immune response
- Resolution

Chronic hepatitis B
- HBeAg (+)
- HBV DNA (+)
- ALT N raised
- Anti-HBe (+)
- HBV DNA (+)
- ALT raised

Resolution

Immunological tolerance

Anti-HBe (+)
HBV DNA (+)
ALT raised

Hepatitis immune response
Viral mutations

Cirrhosis
Hepatic decompensation
HCC

Transplant

- Spontaneous
- Antiviral therapy

Anti-HBe (+)
HBV DNA (-)

Immune control

Immune response
HBeAg positive and negative disease

- **HBeAg positive disease (wild type)**
  - Young individuals with hepatitis B
    - High levels of HBV DNA (usually > $10^7$ copies/ml)
    - May have normal ALT
    - “Immunotolerant phase” of the disease
  - Or with raised ALT in active disease (immuno-active phase)
  - Seroconversion rates higher in patients with raised ALT and genotype B (vs C) and genotype D (vs A)

- Anti-HBe-positive disease
  - HBsAg positive and anti-HBe positive
  - Older
  - HBV DNA typically > $10^5$ copies/ml
  - Genotypic explanations for absent HBeAg
  - Serum ALT elevated
  - Variable course, fluctuating ALT, mixture of wild type and HBeAg negative virus
  - Biopsy shows necro-inflammation and varying fibrosis
Chronic hepatitis B: serological markers
Anti-HBe-positive disease

- HBsAg positive and anti-HBe positive
- Older
- HBV DNA typically $> 10^5$ copies/ml
- Genotypic explanations for absent HBeAg
- Serum ALT elevated
- Variable course, fluctuating ALT, mixture of wild type and HBeAg negative virus
- Biopsy shows necro-inflammation and varying fibrosis
Inactive carrier state

- Spontaneous remission in disease activity
  - HBeAg negative, anti-HBe positive
  - Lower HBV DNA levels (<$10^5$ copies/ml)
- Little or no necroinflammation or fibrosis (depending on timing of seroconversion)
- May be a retrospective diagnosis as some propensity to reactivation
### Prognostic factors for progression to cirrhosis

<table>
<thead>
<tr>
<th>Factors</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>0.0001</td>
</tr>
<tr>
<td>HBV-DNA persistence</td>
<td>0.0001</td>
</tr>
<tr>
<td>Virus genotype C</td>
<td>0.001</td>
</tr>
<tr>
<td>Recurrent acute flares</td>
<td>0.001</td>
</tr>
<tr>
<td>Histologic staging</td>
<td>0.0002</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.001</td>
</tr>
<tr>
<td>HCV, HDV coinfection</td>
<td>0.001</td>
</tr>
<tr>
<td>HIV coinfection</td>
<td>0.02</td>
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</table>

Prognostic factors of survival in cirrhosis B

De Jongh, Gastroenterology 1992; 103: 1630-5

Eurohep, Am J Gastroenterol 2002

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>HBV-DNA + vs HBV-DNA -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>0.89</td>
<td>0.3 - 2.6</td>
</tr>
<tr>
<td>Decompensation</td>
<td>4.0</td>
<td>1.0 - 15</td>
</tr>
<tr>
<td>Liver-related death</td>
<td>5.9</td>
<td>1.6 - 21</td>
</tr>
</tbody>
</table>

HBeAg + vs HBeAg -

\[ p = 0.03 \]  
\[ p = 0.01 \]
Cumulative Incidence of Liver Cirrhosis according to baseline HBV-DNA – Illoeje et al.

Cumulative Incidence of Liver Cirrhosis

Baseline HBV DNA Level, Copies/mL

-4 -3 -2 -1 0

Year of Follow-up

Cumulative Incidence of Liver Cirrhosis

≥ 1.0 x 10^6
1.0-9.9 x 10^5
1.0-9.9 x 10^4
300-9.9 x 10^3
<300
Cumulative Incidence of Decompensated Cirrhosis by Entry HBV DNA

Year of Follow-up

Cumulative Incidence

Decompensated Cirrhosis

≥ 1.0 x 10^5

1.0-9.9 x 10^4

<1.0 x 10^3

EASL 2005
HCC Mortality according to baseline HBV-DNA – *Chen et al.*

Survival Distribution Function

Survival Time (years)

- DNA (-)
- DNA low (+) \( RR=1.8 \ (0.5-5.8) \)
- DNA high (+) \( RR=8.8 \ (3.2-31.0) \)

P for trend <0.01
Liver Disease Mortality according to baseline HBV-DNA – Chen et al.

Survival Distribution Function

Survival Time (years)

DNA (-)
DNA low (+)
RR=1.5 (0.2-11.8)
DNA high (+)
RR=13.4 (1.9-97.1)

P for trend <0.01

EASL 2005
## Incidence and multivariate analysis risk of cirrhosis

<table>
<thead>
<tr>
<th>HBV DNA</th>
<th>Number</th>
<th>Person yr</th>
<th>Number cases</th>
<th>Incidence</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300</td>
<td>944</td>
<td>10,877</td>
<td>42</td>
<td>386</td>
<td>1</td>
</tr>
<tr>
<td>300-9.9x10³</td>
<td>1210</td>
<td>13,926</td>
<td>64</td>
<td>495</td>
<td>1.3</td>
</tr>
<tr>
<td>1.0-9.9x10⁴</td>
<td>649</td>
<td>7,314</td>
<td>58</td>
<td>792</td>
<td>2.2</td>
</tr>
<tr>
<td>1.0-9.9x10⁵</td>
<td>344</td>
<td>3590</td>
<td>66</td>
<td>1838</td>
<td>5</td>
</tr>
<tr>
<td>&gt;1x10⁶</td>
<td>627</td>
<td>6406</td>
<td>165</td>
<td>2757</td>
<td>8.7</td>
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N= 3774

Iloeeje et al, EASL 2005 # 496
Incidence and multivariate analysis risk of HCC Serum HBV DNA in subjects with normal ALT

<table>
<thead>
<tr>
<th>HBV DNA</th>
<th>Number</th>
<th>Person yr FU</th>
<th>Number cases HCC</th>
<th>Incidence</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300</td>
<td>908</td>
<td>10,547</td>
<td>13</td>
<td>123</td>
<td>1</td>
</tr>
<tr>
<td>300-9.9x10³</td>
<td>1178</td>
<td>714</td>
<td>16</td>
<td>116</td>
<td>1.1</td>
</tr>
<tr>
<td>1.0-9.9x10⁴</td>
<td>647</td>
<td>7452</td>
<td>21</td>
<td>281</td>
<td>2.4</td>
</tr>
<tr>
<td>1.0-9.9x10⁵</td>
<td>338</td>
<td>3749</td>
<td>33</td>
<td>880</td>
<td>8</td>
</tr>
<tr>
<td>&gt;1x10⁶</td>
<td>530</td>
<td>5859</td>
<td>60</td>
<td>1024</td>
<td>12.3</td>
</tr>
</tbody>
</table>

N= 3774

Iloeje et al, EASL 2005 # 495
Activity versus Stage

From Hoofnagle et al.
Reducing mortality via treatment: Interferon alpha
Proof of Principle

Long-term Follow-up of Patients With Chronic Hepatitis B Treated With IFN-α

Cumulative Survival

- IFN responders: n = 40
- IFN nonresponders: n = 63

% Surviving

P = 0.004

Reducing mortality via treatment: lamivudine
Proof of Principle

Time to Disease Progression

Placebo (n=215)
YMDDm (n=209) (49%)
Wild Type (n=221)

% with disease progression

0 6 12 18 24 30 36
Time after randomisation (months)

Liaw et al, NEJM 2004
Chronic Hepatitis B

Assessment

- **Clinical features**: hepatitis symptoms, symptoms & signs of decompensation
- **Biochemical**: ALT & other liver tests
- **Virological**: HBsAg, HBeAg, anti-HBe, HBV DNA levels, genotype, mutants
- **Histological**: liver biopsy findings of inflammation, necrosis and fibrosis.
HBV genotypes: Significance

- Far East
  - Genotype B less active disease than genotype C
  - Genotype B lower prevalence of HBeAg
  - Genotype B higher rates of spontaneous seroconversion
  - Genotype B higher rates of response to interferon

- Europe
  - Genotype A higher rates of response than genotype D to interferon

- Probably little, no difference in response to nucleoside analogues

- Genotypes: May affect rate development of lamivudine resistant mutants

- Difference in core promoter vs pre-core mutations
Place of liver biopsy

- Provides unique source of information
- Value being questioned (particularly in HCV)
  - Problems biopsy
    - Low finite risk, but cost and delay and barrier to treatment
- Remains standard for interpretation of disease stage and grade
  - Technological advances may change need for biopsy
- Role in practice will be refined
Indications for treatment
Baseline HBV DNA

- Predicts Disease?
  - As part of spectrum of markers
  - Requires repeated assessments; overlap

- Predicts Prognosis?
  - In part
  - Requires additional assessments of activity

- Predicts Infectivity?
  - Yes

- Provides indication for treatment?
  - Yes, with appropriate clinical and laboratory assessments
HBV DNA
Disease monitoring

- Predicts response to treatment?
  - HBeAg positive:
    - Decline suggests favourable paradigm
    - ? Absolute or relative measures required
  - Anti-HBe positive?
    - Decline suggests favourable paradigm
    - ? Absolute or relative measures required

- Predicts Emergence of Resistance?
  - High viral load associated with resistance
  - Slow decline associated with viral resistance
  - Other complex factors determine resistance
HBV treatment: End points of Antiviral Response:

- HBV DNA decline
- ALT decline
- HBeAg neg
- Anti-HBe
- HBsAg neg

HBeAg Positive

HBeAg Negative

Histology Improves

ccc DNA declines

Variable T cell response
Current Treatments for hepatitis B

- Alpha interferon (Pegylated interferons)
- Lamivudine
- Adefovir Dipivoxil
  - (Tenofovir)
- (Entecavir)
Approaches to therapy of hepatitis B
HBeAg positive and negative

- Finite course of therapy
- Continuous, long-term therapy (indefinite)
- Undefined, depending upon response
Lamivudine

- Lamivudine [(-)-b-L-20,30-dideoxy-30-thiacytidine]
- Nucleoside analogue with antiviral activity.
- Ushered in new era of oral administered antiviral agents
  - New questions raised regarding
    - Indications for treatment
    - End points of treatment
    - Disease monitoring
    - Drug resistance
      - PCR based HBV DNA testing
HBV Lamivudine: 10 year experience

- Pharmacology
- Response
  - Predictors of response
  - Histological response
  - Nature of response
  - Role of genotype
  - Paediatric response
- Immune regulation and lamivudine
- Withdrawal of lamivudine
- Combination therapy
- Resistance
- Clinical course with breakthrough
- Use in transplantation
- Use with chemotherapy
- Use in fulminant hepatitis
- Use in extrahepatic disease
- Use in pregnancy
- Toxicity
- Pharmacoeconomics
The HBV Nucleos(t)ide Pipeline

<table>
<thead>
<tr>
<th>Nucleoside Analogs</th>
<th>Nucleotide Analogs (phosphonates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine (L)</td>
<td>Hepsera (D)</td>
</tr>
<tr>
<td>Entecavir (D)</td>
<td>Tenofovir (D)</td>
</tr>
<tr>
<td>Emtricitabine (L)</td>
<td>Alamifovir (D)</td>
</tr>
<tr>
<td>Telbivudine (L)</td>
<td>Hepavir B (D)</td>
</tr>
<tr>
<td>Clevudine (L)</td>
<td></td>
</tr>
<tr>
<td>Elvucitabine (L)</td>
<td>Activity is not dependent on the first phosphorylation step</td>
</tr>
<tr>
<td>Valtorcitabine (L)</td>
<td></td>
</tr>
<tr>
<td>Amdoxovir (D)</td>
<td></td>
</tr>
<tr>
<td>Racivir (L)</td>
<td></td>
</tr>
<tr>
<td>MIV 210 (D)</td>
<td></td>
</tr>
<tr>
<td>β-L-FddC (L)</td>
<td></td>
</tr>
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</table>

Activity is dependent on first phosphorylation by a host cell nucleoside kinase

Yellow = Prodrug
HBeAg Seroconversion rates

PEG IFN
LDT
ETV-Study 022
LAM-Study 022
ADV-Marcellin 2003
PBO-Marcellin 2003
LAM Consensus (11 References)
LAM Consensus (RCTs†) (4 References)
PBO Consensus (5 References)
PBO Consensus (RCTs) (4 References)

95% CI for Proportion With Seroconversion

*Seroconversion is defined as the proportion of patients with loss of HBeAg and acquisition of HBeAg
†RCTs=Randomized controlled trials

From Dienstag et al EASL 2005 #481
Disadvantage of using monotherapy and engendering resistance

- Treatment failure likely
- Failure associated with exacerbation of disease
- Increase population with resistant strains
- May increase precedent for resistance or deleterious mutations with other agents
- Opportunity cost; drug unusable.
<table>
<thead>
<tr>
<th></th>
<th>Lam</th>
<th>PEG IFN (2a)</th>
<th>Lam 100</th>
<th>Entecavir 0.5 mg</th>
<th>Lam 600, pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>272</td>
<td>214</td>
<td>355</td>
<td>354</td>
<td>463</td>
</tr>
<tr>
<td>Histol Resp*</td>
<td>38%</td>
<td>34%</td>
<td>62%</td>
<td>72%</td>
<td>56</td>
</tr>
<tr>
<td>Log(_{10}) decline</td>
<td>-5.8</td>
<td>-4.5</td>
<td>-5.4</td>
<td>-6.9</td>
<td>-5.5</td>
</tr>
<tr>
<td>DNA &lt; 400*</td>
<td>40 (5) %</td>
<td>25 (14) %</td>
<td>38 %</td>
<td>69 %</td>
<td>40 %</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>20 (19) %</td>
<td>27 (32) %</td>
<td>18 %</td>
<td>21 %</td>
<td>22 %</td>
</tr>
<tr>
<td>Resistance*</td>
<td>27%</td>
<td>ND</td>
<td>18%</td>
<td>2%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*< 200 c/ml LdT, Resistance various defn, Histol response various
Lamivudine resistance HBV

- Incomplete suppression of viral replication
  - Degree of benefit?
  - Is continued therapy beneficial?
- Will selection of increasingly fit, equally pathogenic virus occur by viral adaptation
- Background factors
  - genetic diversity in patients’ viral population
  - HBV genotype
  - HLA type
Adefovir vs Tenofovir: HBV DNA loss

Van Bommel et al Hepatology 2004
Entecavir (ETV)

- Inhibits priming, reverse transcription of (-) strand and synthesis of (+) strand
- Active against LAM-R in vivo but less pronounced against L180M +M204V/I
- 2 dosages developed:
  - 0.5mg in naïve patients
  - 1.0mg in LAM–R patients

1S-(1α,3α,4β)]-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one

HBV Pol Resistance Mutations

Terminal Protein | Spacer | POL/RT

1 183 349 (rt1) 692 (rt 344) 845 a.a.

F__V__LLAQ__YMDD

LMV Resistance: rtL80V/I  rtV173L/rtL180M  rtM204V/I/S
ADV Resistance: rtV84M  rtA181T/V
ETV Resistance: rtV84M  rtA181T/V
L-dT Resistance: rtS184G  rtS202I  rtM204I
ADV + LMV Resistance: rtL180M + rtA181V
TDF Resistance: rtL180M + rtA181V
ABC Resistance: rtH234Y
Disadvantage of using monotherapy drug with high frequency resistance

- Treatment failure likely
- Failure associated with exacerbation of disease
- Increase population with resistant strains
- May increase precedent for resistance or deleterious mutations with other agents
- Opportunity cost; drug unusable.
HBeAg positive patients
Group 1 (High ALT)

- High seroconversion rates > 50%
  - (T cell response)
  - Monotherapy suffices
    - Minority of patients
- But: Patients may not be adversely effected by combination therapy
- Advantage two drugs may give a more predictable response
- *Drawbacks: cost and side effects*
HBeAg positive patients
Group 2 (Not so high ALT)

- Prolonged monotherapy
  - Eventually leads to seroconversion and withdrawal of therapy; resistance?
    - Gradual attrition of cccDNA, invoke T cell response?
- Or prolonged combination therapy
  - Proof of principle of efficacy lacking,
    - proof of reduced resistance shown
  - Difficulty and cost of designing long term trials
    - Eventually leads to seroconversion and withdrawal of therapy
- Or sequential
  - Mistake?
- Piggyback therapy to enhance response
  - criteria for adding therapy?
HBeAg negative disease

- Monotherapy with drugs with low rate of resistance may suffice
- Resistance may still occur but at acceptable rates?
- PEG IFN – Long term suppression rates after finite course?
Current Decision Making Hepatitis B UK

- Treatment form part of the control of the disease
- Disparities in judgements
- Clinical and theoretical paradigms not always reconciled with economic decisions (NICE guidelines)
- Hepatitis B complex disease
  - Clinical care of hepatitis B still evolving
  - Influenced by introduction of new nucleoside and nucleotides
  - Rapid evolution of data
  - Short term studies show effectiveness
  - Longer term studies reduce disease morbidity