Recommendations regarding viral hepatitis care and treatment

Whom to treat - when to treat

VHPB meeting 18 March 2010
Introduction: hepatitis B

- Interferon alpha and recently, the introduction of nucleos(t)ides for therapy of hepatitis B transformed the therapeutic landscape.
- Treatment simpler and safer – but not curative
  - Continued treatment required for most
- Resistance a drawback
- Questions regarding indications for and timing of treatment
HBeAg-positive patients

HBe seroconversion

- PEG-IFN: 30%
- LAM: 22%
- ADV: 22%
- ETV: 26%
- LdT: 21%
- TDF: 12%

Undetectable HBV DNA

- PEG-IFN: 25%
- LAM: 39%
- ADV: 21%
- ETV: 67%
- LdT: 60%
- TDF: 74%

Normal ALT

- PEG-IFN: 39%
- LAM: 66%
- ADV: 48%
- ETV: 68%
- LdT: 77%
- TDF: 69%
Higher viral loads are associated with long-term complications

Progression to Cirrhosis

Progression to HCC

Iloeje UH et al. Gastroenterology 2006; 130: 678–86.

Chen CJ et al. JAMA 2006; 295: 65-73

* Cox proportional hazards models. Risk is relative to <10⁴ copies/mL at entry / not tested at follow up

Data adjusted for gender, age, cigarette smoking and alcohol consumption
Predictors of disease: HIV vs HBV

HIV Treatment necessary and benefit shown

- High viral load ➔ Low CD4 ➔ HIV AIDS

HBV Necessity? Benefit? Health gain? Concerns

- High HBV DNA ➔ ? ➔ Cirrhosis HCC
Chronic hepatitis B: treatment

- Chronic hepatitis B is a life-long disease
- A major health problem in endemic regions
- Treatment should be started with the long-term in mind
- Outcome may be jeopardised by suboptimal treatment

Goals of treatment HBV

- Prevent progression of disease
- Can be achieved by reducing viral load?
  - Level of HBV DNA replication requiring therapy?
  - Optimal target DNA for suppression that alters histology and natural history?
Indications for treatment HBV bon combination of

- Serum aminotransferases
- HBV DNA levels
- Histological stage and activity
Indications for therapy within the guidelines:

HBV DNA >2,000 IU/mL and/or serum ALT >ULN + biopsy or validated non-invasive markers

HBeAg-Positive

The most potent drugs with the optimal resistance profile should be used as first-line monotherapies

HBeAg-Negative

- Indications for treatment must also take into account age, health status, and availability of antiviral agents in individual countries

Indications for therapy
Patients for longitudinal monitoring

- HBeAg positive immunotolerant
  - Most under age 30, normal ALT and high HBV DNA levels without suspicion/family history liver disease
  - Do not require immediate treatment
  - Follow up mandatory

- Patients with mild chronic hepatitis B:
  - ALT < 2X ULN, < A2F2 histologically
  - Do not require immediate treatment.
PCR Negativity At 1 Year

Data not from head-to-head studies

<table>
<thead>
<tr>
<th>HBeAg-positive</th>
<th>HBeAg-negative</th>
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<tbody>
<tr>
<td>PCR Negative (%)</td>
<td>PCR Negative (%)</td>
</tr>
<tr>
<td>ADV1</td>
<td>LAM2</td>
</tr>
<tr>
<td>21%</td>
<td>40%</td>
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Lamivudine monotherapy and cross resistance

LVD monotherapy

A181T/V

L180M

M204V/I

T184S

T184G/S202I/M250V

X

ADV/LdT

ETV

LdT

Preventing resistance nucleoside analogues HBV

- Clear indication for starting therapy
- Encourage patient compliance
- Maximise antiviral activity
- Suppress HBV DNA to lowest possible level
- Maximise genetic barriers
- Avoid sequential treatment
- Avoid treatment interruptions
Indications for treatment: cirrhosis

- Patients with compensated cirrhosis and detectable HBV DNA
  - Considered for treatment
- Patients with decompensated cirrhosis
  - Require urgent antiviral treatment
  - Should be considered for liver transplantation
Changes in HBV DNA cirrhosis

Entecavir

Shim et al J Hepatology 52: 176-182
2 year mortality cirrhosis Entecavir

Shim et al J Hepatology 52: 176-182

Cumulative incidence (%)

Mortality or OLT

HCC

Time (months)

17%

6 %
Utility of nucleosides

- Integral role liver transplantation
  - Combination of nucleosides and HBIG
  - In decompensated disease
  - anti-HBc donors

- Fulminant hepatitis
- Prophylaxis chemotherapy
- Extra-hepatic disease
- HIV co-infected patients
- In pregnancy?
- In HCC (post treatment)?
Nucleosides: Preventing mother infant transmission of hepatitis B

- Vaccination is the mainstay of prophylaxis.
- Utilise antiviral drugs for prophylaxis?
  - What viral level increases the risk of maternal infant transmission despite HBIG and vaccination?
- How early in pregnancy should treatment be initiated?
- Are all nucleos(t)ides safe in pregnancy?
- Which drug is most appropriate?
- What are the risks and benefits for the mother?
# Potential Consequences of Antiviral Drug Resistance in Chronic HBV

<table>
<thead>
<tr>
<th>Category</th>
<th>Consequences</th>
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<tbody>
<tr>
<td><strong>Virologic</strong></td>
<td>Virologic breakthrough and rebound</td>
</tr>
<tr>
<td></td>
<td>Reduced HBeAg seroconversion rates</td>
</tr>
<tr>
<td></td>
<td>HBeAg seroconversion relapse</td>
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<tr>
<td><strong>Biochemical</strong></td>
<td>Biochemical breakthrough</td>
</tr>
<tr>
<td><strong>Histologic</strong></td>
<td>Histologic progression of disease</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Hepatic flare and decompensation</td>
</tr>
<tr>
<td></td>
<td>Increased recurrence post liver transplantation (viral load is strongest predictor of HBV recurrence post liver transplant)*</td>
</tr>
<tr>
<td></td>
<td>Increased tumourigenicity</td>
</tr>
<tr>
<td><strong>Public health</strong></td>
<td>Alteration in HBsAg antigenicity</td>
</tr>
<tr>
<td></td>
<td>Transmission of drug resistant HBV</td>
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<tr>
<td></td>
<td>Development of multi-drug resistant HBV population</td>
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</tbody>
</table>


Treatment forms part of the control of the disease

- Progressive disease is associated with persistence of viral replication and ongoing necro-inflammation

- Remission is associated with loss of active viral replication.
Hepatitis C and liver pathology

- Fibrosis induced by the inflammatory process.
- Factors shown to accelerate the progression to cirrhosis include older age at HCV acquisition, male gender, heavy alcohol intake and co-infection with either HBV or HIV.
- Steatosis may lead to advancing fibrosis.
- No DNA intermediate or integration of viral nucleic acid
- Oncogenesis through cirrhosis and regeneration of liver cells.
Chronic hepatitis C: Evaluating treatment

- The chronic disease generally slowly progressive
- Cirrhosis develops within 20 years in about 10–20%
- Variability in rates of progression of the disease makes the prediction of ultimate outcome difficult.
- The disease is not necessarily benign, however
- The numerical prevalence of the disease has translated into a large pandemic worldwide of liver disease.
Acute hepatitis C

- Clinically mild, and typically unrecognised. Acute hepatitis C is thus only infrequently diagnosed.
- Incidence of acute hepatitis C is falling in several industrialised countries.
- Higher rates of spontaneous recovery from acute hepatitis C have been observed in individuals with identified single nucleotide polymorphisms that lie in or near the IL28B on chromosome 19 which encodes IFN lambda3.
Treatment of acute hepatitis C

• Early identification of acute hepatitis C is important, but may be difficult
• Early spontaneous convalescence can be difficult to confirm
• Recent studies have indicated that treatment benefits those patients who have been treated early.
• The optimal timing and form of treatment for acute hepatitis C is not yet determined but
General management Chronic hepatitis C

- Evaluation of liver disease
- HCV RNA should be quantitated
- Genotype determined
- HBsAg and HIV infection must also be tested
- Liver biopsy or assessment of fibrosis
- Biomarkers: IL28b polymorphisms
- General management
  - Careful clinical monitoring
  - Alcohol: synergistically aggravates hepatic injury.
  - Reversible comorbidities: hepatitis B, HIV, obesity, hepatic steatosis, diabetes, insulin resistance
- Advise on route of transmission and vaccination
**Indications for treatment chronic hepatitis C**

- All patients irrespective of the degree of fibrosis are potential candidates for treatment.
- **Some patients with mild disease do not require immediate treatment**
- Psychiatric co-morbidities may be worsened with IFN treatment: should be stabilised
- Patients with compensated cirrhosis are candidates for treatment
- Alpha IFN is difficult to apply in decompensated cirrhosis and may precipitate deterioration
  - Liver transplantation
Serum aminotransferases and treatment

• Most patients with raised serum ALT are HCV RNA-positive
• The converse not true.
• Perhaps 25-50% may have persistently normal serum ALT.
• “Normal serum aminotransferases" in patients with hepatitis C, frequently actually high relative to healthy individuals.
• Low-grade hepatitis, and even low-grade fibrosis may be present
• Fibrosis progression may be less rapid in females with low or normal ALT.
### Table: Factors adversely determining response

- Genetic polymorphism: tt IL28b polymorphism
- High baseline viral load
- Age greater than 50 years
- High body mass index
- Poor adherence to therapy
- Excess alcohol
- Genotype 1 versus genotype 2 or 3
- Genotype 4, and probably 5 and 6
- Advanced fibrosis, cirrhosis or advanced liver disease
- Hepatic steatosis
- Low platelet count
- High homeostasis model assessment index (HOMA)
- Failure to achieve RVR
- African American ethnicity
- HIV and HCV coinfection
### Impact of disease severity on therapy

- Virological response to re-treatment
- 1046 patients HALT C

<table>
<thead>
<tr>
<th>Group</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
<td>Ishak 3-4 platelets &gt;125</td>
<td>Ishak 3-4 platelets &lt;125</td>
<td>Ishak 5-6 platelets &gt;125</td>
<td>Ishak 5-6 platelets &lt;125</td>
</tr>
<tr>
<td>SVR</td>
<td>23%</td>
<td>17%</td>
<td>10%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Everson Hepatology 44:1675 2006
Overall survival in responders non responders and untreated patients
Decompensated cirrhosis

Iacobellis A et al J Hepatol 46: 206 2007
Other groups for treatment

- IVDU
- HIV coinfected
- Decompensated cirrhosis
- Recurrence post liver transplant
- Non responders
# New agents for hepatitis C

## Anticipated advantages

- Improved response rates
  - Naive and Non responders
- Rapid reduction in HCV RNA
- Shorter duration therapy
- Better tolerated therapy?
- Treatments equally efficacious across all genotypes and subtypes?
- Ribavirin sparing effect?
- Eventual IFN sparing effect?
- Cost effective and cost benefits?

## Potential disadvantages

- New concerns raised
- Unequal effect genotypes and subtypes
- Triple or even quadruple combinations
- Antiviral resistance
- New drug interactions
- Dosing frequency
- Additive or new side effects
- Cost effectiveness
Treatment going forward with new agents

- Mild fibrosis
  - Interferon and RBV
    - Regard these patients as potential candidates
    - Does this hold for new combination therapies?
    - Threat of resistance not previously encountered
- New protocols
  - Standard of care control arms?
Going forward

• Considerable progress has been made in our understanding of hepatitis C infection since its discovery.
• Treatments have also improved, so that more than half of patients with chronic hepatitis C can be cured.
• Newer direct acting antiviral therapies will further improve response rates: Genotype 1: 70% or higher.