Treatment of chronic hepatitis B

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CHRONIC HBV INFECTION

THE DISEASE
Highly heterogeneous at presentation
Variable outcome on long-term
Long-term prognosis uncertain

THE TREATMENT
Valuable therapies available but
  Limited efficacy
  Prolonged administration
  Viral resistance
  High cost

CLINICAL MANAGEMENT DIFFICULT
CHRONIC HEPATITIS B VIRUS INFECTION IS A VERY HETEROGENEOUS CONDITION

- Immuno-tolerant carriers
- Inactive (*healthy*) carriers
- Active carriers
Active HBV carriers

Defined by:
- Elevated ALT
- Increased serum HBV-DNA
- Liver inflammation and fibrosis: Mild, Moderate, Severe

Outcome: Potentially (but not necessarily) progressive disease
- Spontaneous remission possible

Should all active carriers be treated?
Prognostic determinants for chronic hepatitis B in Asians: Therapeutic implications

**CUMULATIVE RISK OF DEVELOPMENT OF COMPLICATIONS**

Good therapies for more seriously ill patients are available

Yuen et al. Gut 2005
Lamivudine for patients with chronic hepatitis B and advanced liver disease

Progression of the disease\(^1\) according to therapy

1: Includes worsening of Child score, clinical decompensation and HCC.

Liaw et al., NEJM 2004
Lamivudine for patients with chronic hepatitis B and advanced liver disease

Progression of the disease according to therapy and development of resistance to lamivudine

Liaw et al., NEJM 2004
Which patients should be treated?

“Therapy should be reserved for those who need to be treated—those with active disease exemplified by raised serum aminotransferases, by clinical or histological evidence of progressive disease, or both. The decision to start therapy should not be made on the basis of HBV-DNA levels alone.....”

Jay H. Hoofnagle
NEJM, March 2006
CRITERIA FOR TREATMENT

- Chronic infection
- HBsAg positive
- Serum HBV-DNA > $10^5$ copies/mL
- Increased ALT
- Liver inflammation (HAI >4)

AASLD, EASL, APASLD Consensus Conferences
Treatment of chronic hepatitis B

Drugs

LICENSED:

- Interferons (alfa-interferon, pegylated $\alpha$-2a interferon)

- Nucleos(t)ide analogues: Lamivudine, adefovir, entecavir, tenofovir (HIV).

ON THE WAY: Telbivudine, clevudine, emtricitabine, pradefovir, valtorcitabine, ANA380....

Combinations

FAR AWAY: Immunostimulants, therapeutic vaccines, gene therapy
### Advantages and disadvantages of available agents

<table>
<thead>
<tr>
<th>INTERFERON</th>
<th>ANALOGUES</th>
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<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>Finite duration of treatment</td>
<td>Side effects. Injection</td>
</tr>
<tr>
<td>Durable response</td>
<td>Low response rate</td>
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<tr>
<td>Loss of HBsAg</td>
<td>Expensive</td>
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<tr>
<td>No resistance</td>
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<tr>
<td><strong>Advantages</strong></td>
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<tr>
<td>Excellent tolerance</td>
<td>Long or indefinite treatment duration</td>
</tr>
<tr>
<td>Oral administration</td>
<td>Drug resistance</td>
</tr>
<tr>
<td>Potent inhibition of viral replication</td>
<td>Low rate of HBsAg clearance</td>
</tr>
<tr>
<td>Less expensive than IFN</td>
<td>Expensive if administered long-term</td>
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</table>
Peginterferon in HBeAg-positive chronic hepatitis B

- Three large controlled trials (1-3)
- More efficient than lamivudine (48 weeks), but less well tolerated
- HBe seroconversion in 30%
- Response sustained in 90% of responders
- HBsAg seroconversion in 3%
- More efficacy in patients with higher ALT, lower serum HBV-DNA and genotype A or B

1) Janssen et al, Lancet 2005
2) Lau et al, NEJMed 2005
Peginterferon alfa-2a in patients with HBeAg-negative chronic hepatitis B

![Bar chart showing HBV-DNA levels after treatment and follow-up.](chart.png)

- **End of treatment (48 weeks):**
  - < 20,000 c./mL: 81 patients (43%)
  - < 400 c./mL: 63 patients (19%)

- **End of follow-up (24 weeks):**
  - < 20,000 c./mL: 43 patients
  - < 400 c./mL: 19 patients

Peginterferon alfa-2a in patients with HBeAg-negative chronic hepatitis B

- 116 patients
  - With biochemical response* after 24 weeks on no therapy.
  - Followed for an additional 18 months (24 months off-therapy)

<table>
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<th>Normal ALT:</th>
<th>44 (38%)</th>
<th>(25%)**</th>
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<tr>
<td>ALT &lt;50 IU/L</td>
<td>47 (41%)</td>
<td>(27%)**</td>
</tr>
<tr>
<td>HBV-DNA &lt; 100x10^3 c./mL</td>
<td>6 (5%)</td>
<td>(3%)**</td>
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HBsAg seroconversion: 6 (5%) (3%)**

*: Defined by ALT below 50 IU/L

**: Percent of the whole treated population

Marcellin et al. EASL 2006 (Abstract 743)
NUCLEOS(t)IDE ANALOGUES

Activity:
Block HBV-DNA polymerase
Chain termination

Effects of one year therapy:
Marked reduction (suppression) of viral replication
Improved ALT, histology and liver function
Well tolerated
Benefits usually not sustained after discontinuation

Prolonged therapy is necessary
For how long?
Resistance may occur
Consequences of viral resistance

- Virologic and biochemical breakthrough
- Loss of initial virologic, biochemical, and histologic response
- Hepatitis flares, hepatic decompensation, and death
Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine

1. HBV DNA < $10^5$ copies/mL by Digene Hybrid Capture II or bDNA Bayer assay
2. Reappearance of HBV DNA by non PCR assay or > $10^5$ copies/mL by PCR assay

AISF Lamivudine Study Group
Long term therapy with Adefovir dipivoxil for HBeAg negative chronic hepatitis B

1. HBV DNA < 1000 copies/mL by Roche Amplicor Monitor PCR assay
2. Detection of ADV-resistance associated mutations

Hadziyannis et al.
NEJM 2005
SUSTAINED BIOCHEMICAL AND VIROLOGICAL REMISSION AFTER DISCONTINUATION OF 4 TO 5 YEARS OF ADEFOVIR DIPIVOXIL TREATMENT IN HBeAg-NEGATIVE CHRONIC HEPATITIS B

33 Patients with HBeAg neg chronic hepatitis B (genotype D)

- In sustained remission under ADV therapy for 4-5 years
  - Normal LFT
  - Undetectable HBV-DNA
  - No genotypic resistance
  - Improved histology
- Followed for 18 months after treatment withdrawal

22 (67%) maintained remission (Inactive HBV carriers)

11 (33%) relapsed within 3 months. Responded to re-treatment

Hadziyannis et al., AASLD 2006, (Abst 114)
Efficacy of one year therapy with nucleosid(t)e analogues for Hepatitis B

Undetectable HBV DNA
(< 400 copies/mL)

ALT Normalization

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<tr>
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<th>HBeAg - Patients</th>
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<tr>
<td>Adefovir</td>
<td>21</td>
<td>51</td>
</tr>
<tr>
<td>Entecavir</td>
<td>69</td>
<td>91</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>38</td>
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<td>Lamivudine</td>
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<td>71</td>
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Entecavir in HBeAg(-) Patients: Week 96

Cumulative Response Outcomes

CURRENT TREATMENT OF CHRONIC HBV INFECTION

- Still evolving
- Effective therapies available
- Optimal therapeutic options partially identified
- Many questions pending