Pharmacological Management of Hepatitis B

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Overview of HBV life cycle and sites of action of Interferons and NRTIs

2 key events in replication

Formation of replicative intermediates ‘covalently closed circular DNA’
Approved HBV Treatments

- Interferon alfa-2b – 1991
- Lamivudine – 1998
- Adefovir – 2002
- Entecavir – 2005
- Peginterferon alfa-2a – 2005
- Telbivudine – 2006
- Tenofovir – 2008

For HIV:
- Emtricitabine
- Tenofovir + emtricitabine (single-pill coformulation)
Interferon (IFN)

- 2 formulations – conventional IFN and PEG-IFN

- IFN has both antiviral & immunomodulatory activity.

- PEG-IFN has superceded conventional IFN because it can be given once a week (cf daily or 3 x per week) and is associated with higher rate of response.

- INF based therapy gradually being replaced by nucleos(t)ide analogues.
HBV Polymerase

Nucleos(t)ide Analogues

- Lamivudine - L-Nucleoside
- Telbivudine – L-Nucleoside
- Adefovir dipivoxil – Acyclic Phosphonate
- Tenofovir disoproxil – Acyclic Phosphonate
- Entecavir – D-Cyclopentane
Lamivudine

- HIV drug; first nucleoside analogue for treatment of Chronic HepB.
- Active drug is 3TC-TP - incorporated into the growing chain of DNA during reverse transcription - *Chain Termination*.
- Effective in suppressing viral replication in both HBeAg-positive and HBeAg-negative patients.
- Major problem is drug resistance – low genetic barrier.
- *Not recommended as the first line treatment for CHB*
Adefovir Dipivoxil

- Approved in 2002.
- Undergoes phosphorylation to adefovir diphosphonate which is incorporated into viral DNA - *Chain Termination*.
- With availability of newer agents ie entecavir and tenofovir with high antiviral efficacy and high genetic barrier, ADV monotherapy is not recommended as first line for treatment naive patients.
- In patients with lamivudine resistance – can add adefovir to lamivudine rather than just switching.

- Concern about renal safety profile.
Adefovir and Tenofovir Interact with Renal Transport Pathways

• The active tubular secretion of adefovir and tenofovir and the transport of creatinine are mediated by distinct transport pathways in renal proximal tubules
Entecavir

- Approved for treatment of CHB in 2005.

- Undergoes phosphorylation to active triphosphate and is incorporated into viral DNA - *Chain Termination*.

- Has high antiviral potency, low resistance rate and good safety profile.

- Recommended as a first line agent for treatment of CHB
# Entecavir

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Value/Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma half life</td>
<td>~130h</td>
</tr>
<tr>
<td>Intracellular half life</td>
<td>~15h</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>~70%. Administer on empty stomach.</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>~13%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Mainly eliminated unchanged by renal excretion</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>Dose modification required</td>
</tr>
</tbody>
</table>
Telbivudine

- Approved in 2006 for treatment of CHB.
- Undergoes phosphorylation to active triphosphate and is incorporated into viral DNA - *Chain Termination*.
- Not recommended as first line treatment due to the high rate of drug resistance with long-term use.
- May have a role in treatment of patients with certain ‘favourable’ characteristics.
- Some reports of elevated serum creatine kinase and myopathy.
Tenofovir

- Initially approved for treatment of HIV
- Approved in 2008 for treatment of CHB
- Undergoes phosphorylation to active diphosphate and is incorporated into viral DNA – *Chain Termination*.
- Tenofovir is more potent than adefovir BUT less nephrotoxic*. Has low resistance rates.
- Tenofovir is recommended as a first line agent for treatment naive patients.
# Tenofovir

<table>
<thead>
<tr>
<th>PK Parameter</th>
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</thead>
<tbody>
<tr>
<td>Plasma half life</td>
<td>(~15)h</td>
</tr>
<tr>
<td>Intracellular half life</td>
<td>(&gt;100)h</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>25%. Can be taken without regard to food.</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>(~0.7)%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Mainly eliminated unchanged by <strong>renal</strong> excretion</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>Dose modification required</td>
</tr>
</tbody>
</table>

**Tenofovir**

The pharmacokinetics of Tenofovir include:

- **Plasma half life**: Approximately 15 hours.
- **Intracellular half life**: Greater than 100 hours.
- **Bioavailability**: 25%. It can be taken without regard to food.
- **Protein Binding**: Approximately 0.7%.
- **Metabolism**: Mainly eliminated unchanged by renal excretion.
- **Renal Impairment**: Dose modification required.
NAs: Potency versus resistance

Entecavir & Tenofovir in Naive Patients: Virological Response

ETV (n=418)

- 6 months: 68%
- 12 months: 85%
- 24 months: 95%
- 36 months: 96%
- 48 months: 99%

TDF (n=302)

- 6 months: 65%
- 12 months: 84%
- 18 months: 91%
- 24 months: 90%
- 30 months: 91%

Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona
Lampertico P et al, AASLD 2011
Antiviral resistance increases over time

Resistance to NAs...is it just a matter of time?


## Recommendations for First-Line Therapy in Patients Without Cirrhosis

<table>
<thead>
<tr>
<th>HBeAg Positive or Negative Chronic HBV</th>
<th>Preferred</th>
<th>Alternative</th>
<th>Not Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>Adefovir</td>
<td>Telbivudine*</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Entecavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg-IFN alfa-2a</td>
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</tbody>
</table>

*HBV DNA must be undetectable at 24 weeks to continue (Keeffe). AASLD guidelines: Lamivudine and Telbivudine not preferred due to relatively high rate of resistance. Adefovir not preferred due to weak antiviral activity and relatively high rate of resistance in HbeAg-negative studies.

Combination Therapy

- Combination therapy is the standard of **HIV** therapy.
- Combination therapy for **HBV** has the potential to:
  - achieve a synergistic antiviral effect
  - sustained loss of detectable HBV DNA
  - improvement in liver histology
  - normalisation of serum ALT
  - reduction in drug resistance.

- The AASLD recommends combination therapy for a select group of patients although to date evidence to support combination therapy in treatment naive patients has not been substantiated. (Cox N & Tillmann H 2011)
Conclusions
Substantial progress has been made in the treatment of hepatitis B in the past decade. Many safe and effective drugs are now available. These drugs suppress but do not eradicate HBV. To optimize treatment response, treatment should be initiated at an appropriate time using the best available drugs, and the response should be closely monitored so that treatment can be modified in patients with treatment failure.
THANK YOU!