“Clinical considerations in HBV management”

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HBV is controllable!

Michael Manns, EASL 2009

Potency of Different Antivirals at 48 to 52 Weeks of Therapy (naïve patients)

Resistance rates through 6 years among nucleos(t)ide-naïve patients

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Characteristics of anti HBV agents in patients naives to antiretrovirals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Genetic barrier</th>
<th>Potency</th>
<th>PK (intracellular levels)</th>
<th>Impact on viral fitness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Entecavir and Tenofovir</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
</tr>
</tbody>
</table>
The paradigm of antiviral therapy is the suppression and maintenance of viremia below the limit of detection.
How to achieve long-term virological success?

Virological response to antiviral drugs is influenced by different factors:

- **Patient**
  - Durability
  - Adherence
  - Convenience and tolerability

- **Drugs**
  - Drug Potency
  - Height and duration of drug exposure
  - Number of mutations required for resistance

- **Virus**
  - Genetic Barrier
  - Baseline Mutations
  - Number and type of mutations present at start of therapy

Legend:
- **Genotype**

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
Management of HBV resistance

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine resistance</td>
<td>* Add tenofovir</td>
</tr>
<tr>
<td>Adefovir resistance</td>
<td>* Switch to tenofovir and add a second drug</td>
</tr>
<tr>
<td></td>
<td>– If N236T, add lamivudine, entecavir* or telbivudine* or switch to Truvada</td>
</tr>
<tr>
<td></td>
<td>– If A181V/T, add entecavir* or switch to Truvada</td>
</tr>
<tr>
<td>Telbivudine resistance</td>
<td>* Add tenofovir*</td>
</tr>
<tr>
<td>Entecavir resistance</td>
<td>* Add tenofovir*</td>
</tr>
</tbody>
</table>
| Tenofovir resistance** | * Do genotyping and phenotyping in an expert lab to determine the cross-resistance profile  
|                     |   * Add entecavir*, telbivudine*, lamivudine or switch to Truvada |

*the long-term safety of these combinations is unknown
**not seen so far


Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
HBV Resistance in a patient treated successively with lamivudine and entecavir


Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Long Term Results in Treatment-naïve patients

ETV-027

Shouval D, et al. AASLD 2008, Poster 927
Chang et al Hepatology 2010; 51:422-430

ETV-901

GS-103 HBeAg (+)

Marcellin P, et al., AASLD 2009; Poster #481.
Heathcote E-J, et al., AASLD 2009; Poster #483.

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Effectiveness of Entecavir For Nuc-Naïve, HBeAg-Negative Chronic Hepatitis B Patients in Clinical Practice: A 2-Year Multicenter Cohort Study in 311 Patients

Virological Response Through Month 30 (HBV DNA < 12 IU/mL)

- 2 (0.6%) patients had a Primary Non Response at week 12
- 19/277 (6%) had a Partial Virological Response

Mixed patient population: HBeAg(+) and HBeAg(–)
Median follow-up: 30 months (range 2–38 months)

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Lampertico P, et al. EASL 2010; Poster # 1009.
• If HBV replication can be suppressed in a sustained manner ... the accompanying reduction in histological activity of chronic hepatitis reduces the risk of cirrhosis and the risk of HCC
  – in non-cirrhotic patients
  – and probably also, but to a lesser extent, in cirrhotic patients
Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus

Long-term ETV treatment achieves histologic improvement in the majority of patients with undetectable HBV DNA

ETV-022 HBeAg(+) 352 Patients
ETV-027 HBeAg(-) 324 patients

Improvement in Knodell HAI score* (Grading)

<table>
<thead>
<tr>
<th></th>
<th>Week 48</th>
<th>Long-term‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>73%</td>
<td>41/56†</td>
<td>55/57</td>
</tr>
</tbody>
</table>

Improvement in Ishak fibrosis score (≥1-point decrease) (Staging)

<table>
<thead>
<tr>
<th></th>
<th>Week 48</th>
<th>Long-term‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>32%</td>
<td>18/56†</td>
<td>50/57</td>
</tr>
</tbody>
</table>

* ≥2-point decrease in Knodell necroinflammatory score and no worsening of Knodell fibrosis score vs baseline.
‡ Median time of long-term biopsy: 6 years (range: 3–7 years).


Subset of 901 rollover study
* Minimum of 3 years, Entecavir therapy
* Adequate baseline and long-term biopsies (57 patients)
* Baseline Knodell necroinflammatory score of ≥2

Hepatology 2008;48: 706A.
Entecavir and tenofovir are potent HBV inhibitors and they have a high barrier to resistance. Thus they can be confidently used as first-line mono-therapies (A1).
EASL Guidelines: Indication for Treatment

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>Hepatitis</th>
<th>Cirrhosis</th>
<th>Decompensated cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>METAVIR</td>
<td>F0 S0</td>
<td>F1 S1-2</td>
<td>F2 S3</td>
</tr>
<tr>
<td>Ishak’s</td>
<td>F1 S1-2</td>
<td>F2 S3</td>
<td>F3 S4</td>
</tr>
<tr>
<td></td>
<td>F2 S3</td>
<td>F3 S4</td>
<td>F4 S5-6</td>
</tr>
</tbody>
</table>

- Elevated HBV DNA levels with or without HBeAg
- ALT level elevation
- Moderate to severe active necroinflammation and/or fibrosis (at least grade A2 or stage F2 by METAVIR scoring)

Need for validation of non-invasive assessment of fibrosis

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*

EASL Guidelines:
Indication for Treatment in Special Populations

Patients with compensated cirrhosis and detectable HBV DNA [even if ALT normal and/or HBV DNA levels < 2000 IU/ml]

Consider therapy

Patients with decompensated cirrhosis

Urgent antiviral treatment is required*

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

* Rapid and profound viral suppression and efficacious prevention of resistance are particularly needed in this group. Significant clinical improvement can be associated with control of viral replication, but patients with very advanced liver disease may not always benefit if treated at this late stage and should be considered for liver transplantation.
Indication to Treatment of HBV is an Integrated Decision

- Treat active virus with active disease
- Do not treat but observe carefully active virus without disease
- Liver Disease Stage
- HBV DNA Levels
- Viral Resistance
- Patient's profile
- Long-term safety
- Cost
- Individualised strategy

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Limitations

- Complexity of host-virus interaction in HBV infection (HBeAg vs anti-HBe phases, immune recognition of virus varies over time and is a determinant of pathogenicity; disease progression is variable)

- All available direct anti-HBV drugs target the same step in viral replication cycle

- Control of HBV-replication does not equal HBV eradication (cccDNA persistence)

- No correlation between antiviral potency and “pathogenetically” relevant end-points (HBeAg loss and anti-HBe seroconversion; HBsAg loss and anti-HBs seroconversion);

- Is lifelong treatment always needed?

- Suppression of HBV replication does not “zero” the risk of HCC (should we treat earlier?)
When to treat?

**HBsAg**

- Immunotolerant phase
- Immuno-active phase
- Inactive phase (Low replication)
- Reactivation phase
- Occult infection

**HBeAg(+) / HBeAg(-) / anti-HBe(+)**

1. **HBV DNA**
   - $10^9 - 10^{12}$ IU/mL
   - $>2000$ IU/mL
   - $<2000$ IU/mL
   - $>2000$ IU/mL

2. **ALAT**
   - Minimal CH
   - Moderate to severe CH
   - Remission
   - Moderate to severe CH

- Cirrhosis
- Inactive cirrhosis
- Treatment indicated
- Treatment indicated

*Adapted from Fattovich G. Sem Liver Dis. 2003*
Therapeutic Strategies

Short-term: “cure”

Follow-up (months/anni)
- IFN / NUC
- On treatment responses
- Anti-HBe+
- HBV DNA < 2000 UI/ml
- ALT < UNL
- Inactive carrier
- HBsAg loss

Long-term: “suppressive” treatment

NUC (s)
- HBV DNA < 15 UI/ml (complete suppression to avoid resistance)
- Inactive Carrier
- HBsAg loss

Years

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What nucleo(s)tide Analogs do not do?

- does not interfere with the establishment of cccDNA in de novo infected hepatocytes
- does not affect cccDNA minichromosome and/or transcription
- does not change cccDNA half life
- BLOCKS CORE PARTICLES RECYCLING (cccDNA pool replenishment ... 1 log decrease /48 weeks)

Once HBV ... forever HBV?


Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Persistence of cccDNA after HBs seroconversion

Maynard et al. J Hepatol 2005
Persistence of cccDNA in patients with long term HBV suppression under lamivudine

Belloni, Levrero, Gaeta  EASL 2010
Limitations

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Are the Endpoints Recommended by Guidelines Achievable?

- **Undetectable serum HBV DNA**
  - Maintained during treatment with NUCs: ~90% after >3-4 yr treatment
  - Sustained after IFN treatment: <20% after 3-4 yr follow-up

- **Durable HBeAg seroconversion in HBeAg+ patients**
  ~50% after 5 yr treatment, durability unknown

- **Sustained HBsAg loss +/- seroconversion to anti-HBs**
  - NUC: 0-2% after 2 yr treatment, durability unknown
  - PegIFN: 11% after 3-4 yr post-treatment follow-up

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
Pros IFN

• Higher anti-HBe seroconversion rate and durability
• Higher HBsAg loss and anti-HBs seroconversion rate

The ideal (PEG) IFN patient

• HBeAg positive
• Low viral load (<10^7 IU/ml)
• High serum ALT (>3 ULN)
• High activity scores liver biopsy (>A2)
• Genotype A


Real world

• In >95% (Germany) or about 85% (Italy) of antiviral HBV therapies NUCs are used
HBsAg Levels During Antiviral Therapy For Chronic Hepatitis B: Peginterferon Versus Entecavir

<table>
<thead>
<tr>
<th>Response at week 48</th>
<th>HBeAg positive</th>
<th>HBeAg negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;400 cp/mL</td>
<td>PEG-IFN (N=61)</td>
<td>ETV (N=33)</td>
</tr>
<tr>
<td>HBV DNA &lt;400 cp/mL</td>
<td>10 (16%)</td>
<td>17 (52%)*</td>
</tr>
<tr>
<td>HBeAg clearance</td>
<td>21 (34%)</td>
<td>3 (9%)*</td>
</tr>
<tr>
<td>HBsAg clearance</td>
<td>6 (10%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*p<0.01


Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Serum HBsAg amounts as surrogate parameter for cccDNA levels

Low serum HBsAg levels correlate with low intrahepatic cccDNA amounts (n=120 biopsies)

Volz, Petersen, Gastroenterology 2007

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
Limitations

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- Is lifelong treatment always needed? (safety and costs) (eradication vs control)

- Suppression of HBV replication does not “zero” the risk of HCC (should we treat earlier?)
Treatment objectives

Accepted end points for treatment discontinuation?

- Improve Histology
- Anti-HBe+
- Negative HBeAg
- Negative HBV DNA
- Improve Survival
- Anti-HBs+
- Negative HBsAg
- TIME
Sustained off-therapy responses in patients with HBeAg(-) CHB who remained in virological remission under ADV for 4-5 years

- 33 patients with HBeAg(-) CHB & HBV DNA<400 cp/mL under ADV for 4-5 years
- Off-treatment F-UP: ≥4 years after stopping ADV
- Sustained biochem. & virol. off-ADV response: 18/33 (55%)
- HBsAg clearance: 9/33 (27%) patients or 9/18 (50%) responders

Hadziyannis SJ et al. AASLD 2008, Abstr. 874
Persistence of cccDNA in patients with long term HBV suppression under lamivudine

 HBsAg

>250  neg  9.4  114

Belloni, Levrero, Gaeta  EASL 2010

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Control of the cccDNA pool during antiviral therapy in CH-B patients

- 1 yr of monotherapy with nucleos(t)ide analogues (ADV, LAM, ETV) reduced median intrahepatic cccDNA amounts by 1 log
  
  Zoulim, Petersen, Locarnini, Gastroenterology 2004
  
  Wong, Antivir Ther 2006

- Intrahepatic cccDNA levels were significantly lower among patients with sustained virological response (LAM, LAM+PEG-IFN)
  
  Sung, Gastroenterology 2005

- One year of combination therapy with PEG-IFN alpha 2b and ADV induced a >2 log cccDNA reduction
  
  Wursthorn, Petersen, Hepatology 2006
Model of cccDNA decline and consecutive HBsAg loss

Cell division in the setting of liver regeneration induced cccDNA destabilization and formation of cccDNA-free cells

Is there a role for signal induced ("non cytolytic") destabilization?

Implications

Not only viral suppression but also some cell injury and compensatory cell growth may be necessary to significantly reduce cccDNA loads in vivo and possibly to achieve control of HBV infection with consecutive reduction or loss of HBsAg

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Combination therapy with IFNα & ADV induced strong intrahepatic HBV DNA reduction

Inhibition of Intrahepatic viral productivity

Lütgehetmann Antiviral Therapy 2008
IFNα inhibits cccDNA transcription

Belloni et al., 2011 (submitted)
Effects of IFNα treatment on HBV replication and transcription in humanized uPA/SCID mice

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus

Belloni et al., 2011 (submitted)

Sustained virological suppression achieved by IFNα treatment (30-35% of HBeAg+ patients and 20-25% of HBeAg- patients, is commonly thought to reflect the transition to the “immune-control” phase that characterize the inactive HBsAg carrier state.

Recent results indicate that IFNα induces a condition of “active epigenetic control” of HBV cccDNA transcription that likely contributes to the persistent, yet reversible, “off therapy” inhibition of HBV replication.
What we want, what we can...

- **HBV suppression**
  - *block HBV DNA synthesis (RT-DNA Pol inhibitors)*
  - *inhibit cccDNA transcription*
  - *target morphogenesis*
  - ......

  Make all active carriers „true“ inactive and, eventually, over time „occult“ carriers

- **HBV eradication**
  - *target cccDNA stability/formation*
  - *block viral entry inhibitors*
  - ......
What I did not mention...

- decompensated cirrhosis
- OLT setting
- HDV co-infection
- HBV-HCV co-infection
- ..... 

- Primary non-response
- Sub-optimal responses
- .....
Conclusions

- suppress persistently replication in CH with significant disease and in all cirrhotic patients

- whenever possible aim at “pathogenetically relevant” endpoints ....

- avoid undue reactivations and sub-optimal antiviral regimens

- remember that the cccDNA is the central molecule and template of HBV replication. A better understanding of the mechanisms that regulate cccDNA function and stability need to be further investigated (bridge with innate/adaptive immune response, signals, pathways, cytokines ... identify new therapeutic targets) .... Combination therapies

- cccDNA clearance is most likely not achievable within the near future .. Possibly, we do not need to clear all cccDNA for a (clinical) cure of HBV patients („epigenetic“ and immune control)

- Need for noninvasive surrogate parameters for cccDNA load/function in patients with hepatitis B (HBsAg quantitation ??)
Laboratory of Gene Expression

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