The role of combination therapy in Hepatitis B

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Is there a role for combination therapy?
Partial virological response during NUC therapy

Check for compliance

In compliant patients with partial virological response under

- LAM or LdT at wk 24 or ADV at wk 48, change (switch!) to a more potent drug (ETV or TDF) preferentially without cross-resistance (A1)

- ETV or TDF at wk 48
  - If HBV DNA levels are declining, continue with the same agent (B1)
  - If HBV DNA levels are not declining, add the other drug in order to prevent resistance in the long term (C2)
Virological breakthrough during NUC therapy

- **LAM resistance**: switch to TDF (add ADV if TDF not yet available) (B1)

- **ADV resistance**: in **NA naive patients** before ADV, switch to ETV or TDF (B1); ETV may be preferred in such patients with high viraemia (C2) in patients with prior LAM-R, switch to TDF and add a nucleoside (C1)

- **LdT resistance**: switch to or add TDF (add ADV if TDF not yet available) (C1)

- **ETV resistance**: switch to or add TDF (add ADV if TDF not yet available) (C1)

- **TDF resistance**: genotyping and phenotyping by an expert laboratory. ETV, LdT, LAM or FTC could be added (C2); switch to ETV may be sufficient if the patient was NA naive before TDF (C2)
Combination HBV therapy is linked to greater suppression in a cohort of infected individuals.

Most patients with HIV do receive fixed combos such as Truvada.
Efficacy of Entecavir With or Without Tenofovir Disoproxil Fumarate for Nucleos(t)ide-Naïve Patients With Chronic Hepatitis B

Comparable efficacy in both arms, a TDF mono arm was missing!
Concl: All treatments were well tolerated in patients with decompensated liver disease due to CHB with improvement in virologic, biochemical, and clinical parameters.
Combination therapy only for a very few patients that do show advanced liver disease and that have failed mono therapy mostly due to resistance to first line NUCs
FROM ADD-ON TO TAKE-OFF IN TREATMENT EXPERIENCED CHRONIC HEPATITIS B PATIENTS WITH VIRAL RESISTANCE OR PARTIAL RESPONSES: FIRST RESULTS OF AN INTERNATIONAL MULTICENTER COHORT STUDY.

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Submitted for EASL 2013
- Is combination therapy bringing us closer to eradication of HBV?

- Role of cccDNA?

- Is combo better for higher rates of HBsAg loss?

- Novel combos?
Once HBV - always HBV?!

Is there a chance to eliminate or silence cccDNA – dividing hepatocytes and cccDNA stability

mod. from S Urban, J Petersen; J Hepatol 2010
Determination of intrahepatic cccDNA loads in proliferating hepatocytes in a mouse model (uPA/SCID mice)

cccDNA decline per infected cell

Intrahepatic cccDNA dilution or loss?

In vivo proliferation of infected hepatocytes induced continuous reduction of cccDNA and significant cccDNA loss in infected livers in the absence of antiviral drugs

Lutgehetmann, Petersen, Dandri, Hepatology 2010
Proposed model of cccDNA decline

Proposed model of cccDNA decline

Clinical implication: cell turnover needed as a prerequisite for cccDNA reduction?

Equal cell division

Cell division in the setting of liver regeneration induces cccDNA destabilization and formation of cccDNA-free cells
Study design: Monocenter open label, HBeAg+ and HBeAg- patients

Triplet liver biopsies were obtained from 16 patients

*Wursthorn, Petersen Hepatology 2006*

*Lütgehetmann, Petersen Antiviral Therapy 2008*
Combination therapy with PEG-IFNα + ADV induced strong intrahepatic HBV DNA reduction
Inhibition of intrahepatic viral productivity by different antiviral regimens

<table>
<thead>
<tr>
<th>rcDNA/cccDNA</th>
<th>Baseline (n=24)</th>
<th>W48 (n=19)</th>
<th>W144 (n=16)</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1000</td>
<td>0</td>
<td>300</td>
</tr>
<tr>
<td>W48</td>
<td>0</td>
<td>200</td>
<td>-99%</td>
</tr>
<tr>
<td>W144</td>
<td>0</td>
<td>0</td>
<td>-99%</td>
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\[p = 0.001\]

How about the more potent NUCs ETV and TDF?

Silencing of cccDNA?

Regulation of cccDNA transcriptional activity?

PEG IFN α2b

Lütgehethmann Antiviral Therapy 2008
Transcription of the HBV cccDNA minichromosome can be regulated epigenetically

Histone acetylation/methylation affects the regulation of gene expression

IFNα treatment is accompanied by a decrease in the acetylation of cccDNA bound H4 histones in vitro

Pollicino et al. Gastroenterology 2006; Levrero et al. J Hepatol, 2009; Belloni, PNAS 2009
Levrero, Dandri, Raimondo, Petersen J Hepatol 2009; Belloni, Levrero, Petersen, Dandri, Raimondo J Clin Inv 2012
Combo therapy in upa mice: viremia

Viremia PEG-IFN

Median viremia reduction after 4 weeks of therapy:
- 1.4Log with Peg-IFN
- 3.4Log with ETV
- 3.3Log with the combination

Suppression in viremia was strongest in the presence of ETV

Allweiss et al EASL2012 submitted
Serological parameters: HBsAg & HBeAg changes

Median HBsAg reduction after 4 weeks of therapy:
- 0.21Log with Peg-IFN
- 0.13Log with ETV
- 0.5Log with combination

Suppression of HBsAg was strongest in the presence of Peg-IFN-α

Allweiss et al EASL2012 submitted
Seroconversion to anti-HBe in 2 patients (months 4 and 7)
All patients remained HBV DNA negative
8 (50%) patients discontinued PEG-IFN, including
5 (31%) for unchanged HBsAg levels at 24-week, and
3 for IFN-related side effects
Switching to PEG-IFN might be sufficient too?

Lampertico et al EASL 2012, Abstract 523
Primary combo, add-on or switch? PEG-IFN plus NUCs

- Adding peginterferon to entecavir increases HBsAg decline and HBeAg clearance – first results from a global randomized trial (ARES-study)  
  Sonneveld et al, AASLD 2012, #19

- Switching from long-term entecavir to peginterferon alfa-2a induces HBsAg seroconversion/HBsAg clearance in HBeAg positive patients  
  Qin Ning et al, AASLD 2012, #216

- PADD-on study, multicenter Germany, main target: to dissect immunological responses, ongoing

- Improved efficacy by individualized combination of PEG IFN a 2a and ADV in HBeAg + chronic hepatitis B  
  Wang et al, Hepatogastroenterology 2012
Towards new treatment targets

Innate responses

Adaptive Immune Responses
## New HBV targets

Additional therapeutic strategies aiming at inhibiting different steps of the HBV life-cycle or mediating host factors are at early stages of development.

<table>
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<tr>
<th>Treatment Type</th>
<th>Status</th>
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<tbody>
<tr>
<td>TLR agonists</td>
<td>(+)</td>
</tr>
<tr>
<td>Cyclophilin inhibitors</td>
<td>(-?)</td>
</tr>
<tr>
<td>HBsAg release inhibitors</td>
<td>(???)</td>
</tr>
<tr>
<td>Entry inhibitors (HBV and HDV)</td>
<td>(+)</td>
</tr>
<tr>
<td>Therapeutic vaccination</td>
<td>(-)</td>
</tr>
<tr>
<td>Prenylation inhibition (HDV)</td>
<td>(-?)</td>
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Acylated HBV preS1-derived peptides block HBV infection in vitro – entry inhibitor

Chemically synthesized lipopeptides derived from the envelope of HBV block virus infection in cell culture (HepaRG & PTH, PHH)

Grippon et al., PNAS, 99 (24) 2002
Urban et al., J. Virol, 79 (3), 2005
Glebe et al., Gastroenterology, 129, 2005
Engelke et al., Hepatology, 43, 2006
Schulze et al., Hepatology, 46, 2007
Administration of Myrcludex B prevents the establishment of de novo HBV infection in vivo; Phase I studies completed, IIa recruiting

Might be interesting to combine with PEG-IFN and/or NUCs

Petersen, Dandri et al. Nature Biotech. 2008
Conclusions

- Mono therapy either with NUCs or PEG IFN is the therapy of choice for the great majority of chronically infected HBV patients in 2012
- The combination of ETV plus TDF is only required in a very few clinical situations such as true drug resistance and advanced liver disease
- Combination therapy with NUCs and PEG IFN have shown to greater reduce the amount of cccDNA and HBsAg
- There might be room for combo therapy in the future for a higher chance of clinical cure (HBsAg loss)
Thank you for your attention

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Disclosures

My presentation includes off-label use of combination therapies (different NUCs and NUCs plus PEG-IFN)

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