Novedades en el tratamiento de la hepatitis B: noticias desde la EASL

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Milestones in CHB treatment

Conventional IFN 1991
Lamivudine (LAM) 1998
Adefovir (ADV) 2002
Entecavir (ETV) 2005
PEG-IFN 2005
Telbivudine (LdT) 2006
Tenofovir disoproxil fumarate (TDF) 2008

http://www.hepb.org/patients/hepatitis_b_treatment.htm

IFN: interferon; PEG-IFN: pegylated interferon
HBV DNA replication can be successfully controlled, with little or no resistance

<table>
<thead>
<tr>
<th>Response</th>
<th>ETV</th>
<th>TDF</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HBeAg+ patients</td>
<td>HBeAg- patients</td>
</tr>
<tr>
<td></td>
<td>Year 5¹</td>
<td>Year 3²,*</td>
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<tr>
<td>HBV DNA suppression†</td>
<td>94% (88/94)</td>
<td>95% (54/57)</td>
</tr>
<tr>
<td>Resistance</td>
<td>1% (n=1)</td>
<td>NR</td>
</tr>
<tr>
<td>HBsAg loss (seroconversion)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Note: These are not head-to-head studies.

¹ETV re-treatment (relapsed <6 months post-treatment in ETV-027 study); ²For ETV: HBV DNA <300 copies/mL; for TDF: HBV DNA <29 IU/mL (<400 copies/mL); for IFN <400 copies/mL.

ETV: entecavir; HBeAg: hepatitis B ‘e’ antigen; LAM: lamivudine; NR: not reported; PEG-IFN: pegylated interferon; TDF: tenofovir disoproxil fumarate

2. Shouval D, et al. Hepatology 2008;48(suppl S1):722A (Poster #927);
Liver fibrosis regression and cirrhosis reversal over 5 years of TDF treatment

- TDF vs ADV for 48 weeks then open-label TDF in HBeAg− and HBeAg+ patients (Studies 102 and 103)
  - 348 had biopsies at baseline and Year 5; 96 with cirrhosis
  - Multivariate analysis: only low BMI associated with fibrosis regression at Year 5
  - 74% (71/96) had reversal of cirrhosis


Histologically evaluable patients in the long-term histology cohort
344 patients had biopsies at baseline, Year 1 and Year 5.
Transient elastography to assess change in liver inflammation and fibrosis during antiviral therapy

- 599 adult treatment-naïve patients with HBeAg+ CHB (347 with paired biopsy) enrolled in the EFFORT STUDY
  - HBV DNA ≥5 log₁₀ copies/mL
  - ALT 2–10 x ULN
  - LdT ± ADV for up to 260 weeks (5 years)

Liver stiffness

- 24- and 52-week liver stiffness associated with improvements at 104 weeks
  - Necroinflammation (Knodell ≤2; OR, 1.889; P=0.014)
  - Fibrosis (Ishak ≤2; OR, 3.002; P=0.023)

Sun J, et al. EASL 2016; Oral #GS02. BL: baseline; LdT: telbivudine; OR: odds ratio; ULN: upper limit of normal
Treatment discontinuation after HBsAg loss is safe in chronic hepatitis B patients treated with nucleos/tide analogs: A retrospective multicenter study (HEBESAS)

- **AIM:** To assess clinical, biochemical, serological, and virological outcomes in patients with treatment discontinuation after HBsAg loss
- **HEBESAS:** Observational, retrospective, multicentre study in patients with CHB treated with NUCs with HBsAg loss

### Demographics (N=69)
- Mean age 52 years
- Male n=63 (91%)
- HBeAg-positive n=35 (51%)
- Median HBV DNA $1.78 \times 10^6$ IU/mL
- Fibrosis F3–F4 n=10 (29%)

### At treatment discont. (median 11.3 months):
- HBV detectable in n=6/68 (9%)  
  - ALT mean $26.8 \pm 24.2$ U/L  
  - Anti-HBs positive n=34/63 (54%)

### At end of follow-up (median 24.8 months):
- HBV detectable in 1 patient  
  - ALT mean $23.1 \pm 17.5$ U/L  
  - Anti-HBs positive n=54/63 (86%)  
  - No HBsAg seroreversion

Suárez E, et al. EASL 2016, Barcelona. FRI-113
Long-term antiviral therapy reduces the incidence of HCC

- 5908 CHB patients (US medical institutions, REVEAL-HBV study)
- 973 patients received antiviral therapy (47% ETV; 22% TDF) (US medical institutions)

- 77% risk reduction with treatment ($P<0.0001$)

Yang HI, et al. AASLD 2015; Oral # 207.

Oral antiviral therapies are not indicated to prevent HCC development.
Abnormal ALT levels after starting ETV associated with a higher risk of HCC

578 treatment-naive patients with HBV associated cirrhosis were treated with ETV for more than 1 year. 81 patients (14%) developed HCC during follow-up.
Are NAs carcinogens or anti-carcinogens?

Mice

Entecavir 4mg daily

Lung adenomas and carcinomas

HCC

Vascular tumors

Increased incidence of malignancies in CHB patients receiving long-term oral NA therapy

Wong GL-H, et al. EASL 2016; Oral #PS052. aHR: adjusted hazard ratio

↑ Risk of colorectal cancer versus control
(aHR: 2.17; 95% CI: 1.08, 4.36; P=0.029)

↑ Risk of cervical cancer versus control
(aHR: 4.41; 95% CI: 1.01, 19.34; P=0.049)

↔ Risk of other malignancies versus control

Retrospective study of 45,299 CHB patients

NA therapy
(n=7323)

Control
(n=37,976)

Median follow-up = 4.4 years

5.7%
(n=274)

2.1%
(n=538)

Incident malignancies (other than HCC)

Primary outcome

Wong GL-H, et al. EASL 2016; Oral #PS052. aHR: adjusted hazard ratio
Risk of recurrence in HBV related HCC patients failed in NUCs secondary prevention. A Nationwide cohort study

21,197 HCC cases received curative surgical resection as first line therapy, 941 patients received NUCs for CHB after surgery

Lee IC et al EASL 2016. S327
## New treatment options in HBV infection – Phase III

<table>
<thead>
<tr>
<th>Author</th>
<th>Substance (Company)</th>
<th>Class</th>
<th>Phase</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Buti M et al. (GS06)</td>
<td>Tenofovir alafenamide (Gilead)</td>
<td>NUC</td>
<td>Phase III</td>
<td>HBeAg negative</td>
</tr>
<tr>
<td>Chan H Y-L et al. (GS12)</td>
<td>Tenofovir alafenamide (Gilead)</td>
<td>NUC</td>
<td>Phase III</td>
<td>HBeAg positive</td>
</tr>
</tbody>
</table>
Tenofovir alafenamide (TAF) for the treatment of chronic hepatitis B
Agarwal K et al. J Hepatol 2015; 62: 533–540

- Tenofovir alafenamide (TAF)
  - New tenofovir (TFV) prodrug; greater plasma stability than TDF
  - Enhances delivery of active drug (TFV-DP) to hepatocytes
  - Reduces circulating levels of TFV relative to TDF
  - Improved bone and renal safety?

TAF diff. dosages
TAF Phase III Results: Primary Endpoint (HBV DNA <29 IU/mL)
Study 108 and 110

HBeAg negative
Study 108, Buti M et al.

HBeAg positive
Study 110, Chan H Y-L et al.

Results: ALT Normalization
Study 108 (HBeAg negative patients)

![Graphs showing ALT normalization over time.](image)

Central Laboratory
- TAF: 83%
- TDF: 75%

AASLD Laboratory Criteria
- TAF: 50%
- TDF: 32%

Central lab upper limit of normal (ULN): males ≤43 U/L, females ≤34 U/L (≥69 y, males ≤35 U/L, females ≤32 U/L); AASLD criteria ULN: males ≤30 U/L, females ≤19 U/L.

Butl Met al. GS06/EASL_ILC 2016
### Results: Serology at Week 48

Study 110

<table>
<thead>
<tr>
<th>Patients, n/n (%)</th>
<th>TAF n=581</th>
<th>TDF n=292</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss</td>
<td>78/565 (14)</td>
<td>34/285 (12)</td>
<td>0.47</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>58/565 (10)</td>
<td>23/285 (8)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>HBsAg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss</td>
<td>4/576 (&lt;1)</td>
<td>1/288 (&lt;1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>3/576 (&lt;1)</td>
<td>0</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Chan H et al EASL 2016
Changes in Spine and Hip BMD Through Week 48
Study 108

Fewer TAF patients had >3% decreases in BMD at Week 48
- Spine: 22% TAF; 39% TDF (p <0.001)
- Hip: 10% TAF; 33% TDF (p <0.001)
Bone Biomarkers Over 48 Weeks
Study 108

C-Type Collagen Sequence (Resorption)

Procollagen Type 1 N-Terminal Propeptide (Formation)

Osteocalcin (Formation)

Bone-Specific Alkaline Phosphatase (Formation)

p <0.001

p <0.001

p <0.001

p <0.001

TAF

TDF

♦ Minimal changes in bone turnover markers with TAF
**Results: Renal Safety at Week 48**

**Study 108**

<table>
<thead>
<tr>
<th></th>
<th>TAF n=285</th>
<th>TDF n=140</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sCr change, mg/dL</strong></td>
<td>0.012 (0.091)</td>
<td>0.020 (0.103)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>eGFR&lt;sub&gt;CG&lt;/sub&gt; change, mL/min</strong></td>
<td>-1.4 (12.7)</td>
<td>-4.7 (12.0)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>No proteinuria by dipstick n/n (%)</strong></td>
<td>221/282 (81)</td>
<td>114/140 (81)</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Confirmed renal events, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCr ≥0.5 mg/dL from baseline</td>
<td>1 (&lt;1)*</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>eGFR&lt;sub&gt;CG&lt;/sub&gt; &lt;50 mL/min</td>
<td>1 (&lt;1)*</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>PO&lt;sub&gt;4&lt;/sub&gt; &lt;2.0 mg/dL</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*52-year-old man with hypertension and diabetes mellitus had increased sCr and decreased eGFR<sub>CG</sub> at week 44; both events resolved without interruption in study treatment.

Continuous data are expressed as mean (SD).

sCr, serum creatinine; eGFR<sub>CG</sub>, creatinine clearance by Cockcroft-Gault; PO<sub>4</sub>, serum phosphate.
Results: Quantitative Proteinuria Markers at Week 48

Study 108

- Minimal changes in markers of proximal tubular proteinuria with TAF

- Median (Q1, Q3) Change From Baseline, %
  - Protein (UPCR): 5.5 (21.3)
  - Albumin (UACR): 0.5 (7.0)
  - Retinol-Binding Protein: 26.3
  - β2-Microglobulin: 35.9

(TAF: purple, TDF: green)
Conclusions

♦ In treatment naïve and experienced HBeAg-negative and HBeAg positive patients with CHB, treatment with TAF for 48 weeks demonstrated:
  – Non-inferior efficacy to TDF in the proportion with HBV DNA <29 IU/mL
  – Improved rates of serum ALT normalization

♦ TAF was safe and well tolerated in CHB patients
  – Treatment-emergent AEs were similar to TDF
  – Significantly less declines in BMD of hip and spine compared to TDF with improved bone biomarkers
  – Significantly smaller decreases in eGFR$_{CG}$ compared to TDF with improved markers of renal tubular function
## New treatment strategies in HBV infection – experimental/early clinical

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<tr>
<td>Yuen M-F et al. (LB06)</td>
<td>NVR3-778 (Novira Therapeutics)</td>
<td>Core inhibitor</td>
<td>Phase 1b</td>
</tr>
<tr>
<td>Mani N et al. (THU-198)</td>
<td>AB-423 (Arbutus Biopharma)</td>
<td>Capsid assembly inhibitor (small molecule)</td>
<td>preclinical (mice)</td>
</tr>
<tr>
<td>Li P-C et al. (FRI-136)</td>
<td>CpAMs (Assembly Biosciences)</td>
<td>Core protein assembly modulators</td>
<td>preclinical</td>
</tr>
<tr>
<td>Yuen M-F et al. (THU-193)</td>
<td>ARC-520 (Arrowhead Pharmaceuticals)</td>
<td>siRNA</td>
<td>Phase IIa</td>
</tr>
<tr>
<td>Xu Z et al. (THU-213)</td>
<td>ARC-520 (Arrowhead Pharmaceuticals)</td>
<td>siRNA</td>
<td>Chimps</td>
</tr>
<tr>
<td>Blank A et al. (PS054)</td>
<td>Myrcludex B (Maxwell Biotech)</td>
<td>Entry inhibitor</td>
<td>Phase 0/1</td>
</tr>
</tbody>
</table>
HBV life cycle

- HBV virion
- NTCP (receptor)
- HBV enters cell
- Vesicular transport to Golgi and cell membrane
- Multivesicular body
- DNA synthesis
- Intracellular amplification
- Core assembly
- RNA packaging
- Protein-free viral DNA
- cccDNA
- Repair
- Transcription
- pgRNA Core Pol
- Intermediate Compartment
- Surface antigen
- Endoplasmic reticulum
- Nucleus
- Cytoplasm

Courtesy Mani N et al. Poster THU-198/EASL ILC 2016
Inhibition of HBV capsid assembly and pgRNA encapsidation are well validated targets

AB-423 a potent small molecule inhibitor of HBV capsid assembly (Mani N et al.)

GLS-4 capsid assembly inhibitor (Bassit L et al. LB050/EASL_ILC 2016)

NVR-3-778 core inhibitor

HBV DNA decline with highest dose (600mg): 1.72 log, and plus pegIFN: 1.97 log

(Yuen M-F et al. LB06/EASL_ILC 2016)

Retrotranscription + DNA replication
rcDNA-containing nucleocapsid

Courtesy Mani N et al. Poster THU-198/EASL_ILC 2016; modified
RNAi therapeutics vs. reverse transcriptase inhibitors (NUCs) for treatment of chronic HBV

- HBV Virion Infection
- Hepatocyte: Nucleus, HBV DNA, Viral Protein Production, mRNA
  - Viral Antigens: HBSAg, HBeAg
  - Reduced Viral Replication
  - Immune Suppression Unchanged
  - Reduction/Elimination of Reinfecion, Contagion

- HBV Virion Infection
- Hepatocyte: Nucleus, HBV DNA, Reduced Viral Protein Production, mRNA
  - Reduced Viral Replication
  - Immune Suppression Unchanged
  - Reduced Viral Antigens
  - Reversal of Immune Suppression
  - HBsAg seroconversion & functional cure

NUCs

ARC-520

Poster THU-213

Courtesy Xu Z et al. Poster THU-213/EASL_ILC 2016
HBsAg reduction in naïve HBeAg positive and negative patients with chronic HBV after RNA interference therapy with ARC-520

- Two distinct patterns of HBsAg reduction
  - HBeAg positive:
    - Immediate antiviral effect
    - Max 1.8 log, mean 1.5 log reduction
    - Still reduced at day 85
  - HBeAg negative:
    - Delayed response
    - Max 0.5 log, mean 0.3 log reduction

Hepatitis delta virus (HDV) kinetics under the prenylation inhibitor lonafarnib suggest HDV-mediated suppression of HBV replication

Cihan Yurdaydin¹, Nathaniel Boruchov², Cagdas Kalkan¹, Swati DebRoy²,³, Christopher Koh⁴, Ersin Karatayli¹, V Haynes-Williams⁴, Senem C. Karatayli¹, Laetitia Canini²,⁵, Susan L. Urichard², A Mihat Bozdayi¹, Theo Heller⁴, Scott J. Cotler², Ramazan Idilman¹, Jeffrey S. Glenn⁶, and Harel Dahari¹

**Fig. 1A**

Patient 2: Lonafarnib 100mg bid + 100mg Ritonavair

Yurdaydin C et al. FRI-111/EASL_JLC 2016