Currently status of HBV therapy: efficacy and limitations

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Outline of the presentation

- Endpoints and goal of HBV therapy
- Peg-IFN, ETV, TDF as monotherapies
- PEG+IFN and NUC combination
- Long-term outcome: histology, ESLD, HCC and death
- Limitations of current therapies
The decision to treat is historically based on phase of disease and risk of disease progression

<table>
<thead>
<tr>
<th>Phase</th>
<th>Immune tolerant</th>
<th>HBeAg-positive CHB</th>
<th>Inactive carrier</th>
<th>HBeAg-negative negative CHB</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg status</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Very high</td>
<td>&gt;2000 IU/mL</td>
<td>&lt;2000 IU/mL</td>
<td>&gt;2000 IU/mL (fluctuating)</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>Elevated</td>
<td>Normal</td>
<td>Elevated (fluctuating)</td>
</tr>
<tr>
<td>Liver histology</td>
<td>Normal or mild</td>
<td>Inflammation</td>
<td>Normal or mild</td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td>inflammation</td>
<td>and fibrosis:</td>
<td>inflammation</td>
<td>and fibrosis:</td>
</tr>
<tr>
<td></td>
<td>and limited</td>
<td>degree varies</td>
<td>degree varies</td>
<td>degree varies</td>
</tr>
<tr>
<td>Disease progression</td>
<td>Low</td>
<td>Moderate to high</td>
<td>No, very low</td>
<td>Moderate to high</td>
</tr>
<tr>
<td>Treatment</td>
<td>Not indicated*</td>
<td>Indicated</td>
<td>Not indicated</td>
<td>Indicated</td>
</tr>
</tbody>
</table>

* Treatment indicated in some patients

Studies in patients and humanized mice indicate that combination treatments suppressing both HBV replication (NUCs) and cccDNA transcription (IFNα) may trigger significant antigen decline (HBe and HBs) – combination needs to be done in a smart way.

Adapted from Thimme & Dandri, J Hepatol 2012;58:205-9
What can we achieve with Peg-IFN alfa-2a in CHB?

- Treatment aims to enable patients to achieve inactive CHB with sustained immune control

Approximately 30% of patients respond to treatment with Peg-IFN alfa-2a

- Peg-IFN alfa-2a treatment can also result in off-treatment immune control
- Potential long-term clinical benefits of sustained immune control after a finite course of Peg-IFN alfa-2a therapy:
  - Freedom from potentially life-long treatment
  - No long-term safety concerns
  - Decreased risk of cirrhosis and liver cancer
  - HBsAg clearance (clinical cure)

How can we improve PEG-IFN efficacy? 

**Summary**

- Baseline predictive scores (4-5 variables) *(YES)*
- Baseline genetic predictors of HBsAg loss *(unclear)*
- Week 12-24 stopping rules based on HBsAg levels *(YES)*
- Extend duration of IFN to 96 wks for geno D *(YES)*
- NUC pretreatment for HBeAg pos pts *(NO)*
- *De-novo* PEG-IFN+TDF *(few patients, GT A ?)*
5 years ETV for real life, naive CHB patients

Virological summary

<table>
<thead>
<tr>
<th>Region</th>
<th>Virological Success</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>97%</td>
<td>n=744</td>
</tr>
<tr>
<td>Italy</td>
<td>99%</td>
<td>n=418</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>97%</td>
<td>n=222</td>
</tr>
<tr>
<td>Japan</td>
<td>100%</td>
<td>n=252</td>
</tr>
<tr>
<td>China</td>
<td>100%</td>
<td>n=117</td>
</tr>
<tr>
<td>Thailand</td>
<td>96%</td>
<td>n=535</td>
</tr>
</tbody>
</table>

References:
6) Tanwandee T, et al. Hepatology 2013;58:672A
3-4 years TDF for real life, naive CHB patients
Virological summary

<table>
<thead>
<tr>
<th>Country</th>
<th>Virological Success</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>92%</td>
<td>n=184</td>
</tr>
<tr>
<td>France</td>
<td>94%</td>
<td>n=440</td>
</tr>
<tr>
<td>Spain</td>
<td>100%</td>
<td>n=180</td>
</tr>
<tr>
<td>Europe</td>
<td>97%</td>
<td>n=374</td>
</tr>
</tbody>
</table>

ETV or TDF therapy for CHB - Limitations

- Partial response in HVL patients (NUC-R ?)
- Safety issues in selected TDF treated patients
- Low HBeAg/HBsAg seroconversion rates
- Limited stopping rules (HBsAg seroconversion ?)
- Long duration of therapy
- Cost, compliance, resistance, safety > 8 years ??
- Young patients with mild liver disease
Registration studies (8 years) showed minimal renal events on TDF

Real-life studies with TDF showed controversial results

8 cases of TDF-induced Fanconi syndrome have been described

Higher risk of TDF renal toxicity in older patients, previously exposed to ADV, with comorbidities, longer duration of TDF

Need for more research with more sensitive markers of tubular damage
Tenofovir Alafenamide (TAF) Prodrug of TFV – Reduces Circulating TFV

- TAF is more stable in plasma compared with TDF\(^1\)-\(^2\)
- TAF 25 mg has 92% lower circulating plasma TFV levels compared to TDF 300mg\(^1\)

\(^1\)\( T_{1/2} \) based on \textit{in vitro} plasma data
Agarwal K et al. \textit{J Hepatology} 2015; 62: 533-540
TAF vs TDF in naive patients with CHB
A 48-week phase III study

(Authors’ Conclusions)

- Treatment with TAF for 48 weeks demonstrated:
  - Non-inferior efficacy to TDF for the proportion with HBV DNA <29 IU/mL
  - Improved rates of ALT normalization
  - No resistance development in either treatment group
  - Rates of HBeAg loss and seroconversion similar to TDF in Study 110

- TAF was safe and well tolerated in HBeAg-neg and -pos patients
  - Treatment-emergent AEs similar to TDF
  - Significantly less declines in hip and spine BMD compared to TDF, with improved bone biomarkers
  - Significantly smaller increases in sCr (integrated safety analysis) and decreases in eGFR<sub>CG</sub> compared to TDF, with improved markers of renal tubular function

Combination of NUC and PEG-IFN?
A systematic review

- NUC to improve IFN response in naive patients
  - Sequential NUC to IFN (NO)
  - De-novo NUC + IFN combination (few patients, GT A ?)

- IFN to improve NUC response in naive patients
  - “Early” add-on IFN for HBeAg pos pts (??)
  - De-novo NUC + IFN combination (few patients, GT A ?)

- IFN to improve NUC response in treated patients
  - “Switch” NUC to IFN in HBeAg pos (YES in few patients)
  - “Add-on” IFN to NUC in HBeAg neg (YES in few patients)

When to stop NUC therapy?

<table>
<thead>
<tr>
<th>CHB Treatment Guidelines</th>
<th>EASL 2012 guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg positive</td>
<td>A) confirmed anti-HBe seroconversion (and undetectable HBV DNA) after at least 12 months of consolidation*</td>
</tr>
<tr>
<td></td>
<td>B) confirmed HBsAg loss and anti-HBs seroconversion</td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>confirmed HBsAg loss and anti-HBs seroconversion</td>
</tr>
<tr>
<td>Cirrhotics</td>
<td>confirmed HBsAg loss and anti-HBs seroconversion</td>
</tr>
</tbody>
</table>

*A proportion of patients who discontinue NUC therapy after anti-HBe seroconversion may require retreatment, since they fail to sustain their serological and/or virological response.

adapted from EASL HBV Guidelines, J Hepatol 2012; Reijnders JG and Janssen HL. Hepatology 2013, EASL Special HBV conference, J Hepatol 2015
Virological remission after NUC discontinuation in HBeAg pos CHB - A systematic review

14 studies, 733 initially HBeAg+ patients

HBV DNA <20,000 IU/mL, (% pts)

- 6 months: 73.4%
- 12 months: 62.5%
- 24 months: 53.4%
- 36 months: 51.5%

Pooled HBsAg loss: 1%; Durable biochemical remission: 76%

Papatheodoridis G. et al, Hepatology 2016
Virological remission after NUC discontinuation in HBeAg neg CHB - A systematic review

Pooled HBsAg loss: 1.7%; Durable biochemical remission: 57%

Papatheodoridis G. et al, Hepatology 2016
Long-term clinical benefits
5-year TDF treatment - Histological outcomes: liver fibrosis regression and cirrhosis reversal

- TDF vs ADV for 48 weeks then open-label TDF in HBeAg- and HBeAg+ patients (Studies 102 and 103)
  - N=348 had biopsies at baseline and Year 5
  - N=96 with cirrhosis
- 74% (71/96) had reversal of cirrhosis
- Only low BMI was associated with fibrosis regression at Year 5
- Baseline BMI, diabetes at baseline and on-treatment ALT level associated with cirrhosis reversal

Does long-term NUC therapy prevent decompensation in cirrhotics?

▶ ETV: 3-5 years real life cohort studies in Europe and Asia (1-4)

▶ TDF: 3-4 years real life cohort studies in Europe (5-6)

Decompensation is fully prevented in ETV or TDF treated compensated cirrhotics (if HBV in the only aetiology !)

HCC in HBV: a challenging issue

- Complex pathogenesis (single cell event)
- Multiple risk factors (host, virus, interactions)
- Long time elapsed between first cell committed and diagnosis
- Study design (RCT, retrospective, prospective, cohort..)
- Patient selection (with or without cirrhosis, NUC-naïve….)
- Controls (????, all cirrhotics treated since 1996 !!)
- Duration of therapy (> 5 years ETV/TDF….)
- Competitive causes of liver-related death
### Long-term NUC and prevention of HCC
### Propensity score studies from Asia and US

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Follow-up (yr)</th>
<th>% HCC at 5 yr</th>
<th>RR (95% C.I.)</th>
<th>P-value</th>
</tr>
</thead>
</table>
| Wu et al<sup>1</sup>  
(Taiwan)     | 21,595   | 21,595         | 3.4           | 5.2           | 7.3     | 22.7    | 0.31 (0.27–0.53) | <.001 |
| Hosaka et al<sup>2</sup>  
(Japan)     | 316      | 316            | 3.3           | 7.6           | 3.7     | 13.7    | 0.37 (0.15–0.91) | .03   |
| Kumada et al<sup>3</sup>  
(Japan)     | 117      | 117            | 12.3          | 11.6          | 2.7     | 11.3    | 0.28 (0.13–0.62) | .002  |
| Gordon et al<sup>4</sup>  
(United States) | 820      | 1,851          | 5.2           | 5.2           | n.a.    | n.a.    | 0.48 (0.27–0.86) | <.01  |

n.a. = not available

The PAGE-B study
HCC in ETV/TDF treated pts beyond year 5

HCC beyond yr-5 associated only with older age (p=0.062) or age ≥55 at ETV/TDF onset (p=0.02)

Papatheodoridis G, Lampertico P et al. AASLD 2015
Survival
ETV treatment reduces deaths in HBV cirrhotics
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**Liver-related mortality**

- Untreated controls
- NUC-non responders
- NUC-responders

**All-cause mortality**

- Maintained viral suppression achieved ($P < 0.001$)
- No maintained viral suppression ($P = 0.57$)
- Control cohort

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Wong et al, Hepatology 2013;58:1537-1547
The PAGE-B study
Causes of deaths in ETV/TDF treated patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (N=1815)</th>
<th>No cirrhosis* (n=1269)</th>
<th>Cirrhosis* (n=503)</th>
<th>*P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver unrelated deaths</td>
<td>33 (1.8%)</td>
<td>17 (1.3%)</td>
<td>14 (2.8%)</td>
<td>0.059</td>
</tr>
<tr>
<td>Liver related deaths</td>
<td>21 (1.2%)</td>
<td>4 (0.3%)</td>
<td>15 (3.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>in patients with HCC</td>
<td>16/85 (18.8%)</td>
<td>4/26 (15.4%)</td>
<td>10/57 (17.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>in patients without HCC</td>
<td>5/1730 (0.3%)</td>
<td>0/1243 (0%)</td>
<td>5/446 (1.1%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- The 5-yr survival of Caucasian CHB patients treated with ETV/TDF is excellent (>95%)
- A significant proportion of deaths comes from liver unrelated causes.
- HCC development is a major factor affecting the overall mortality and the only factor affecting liver related mortality in such patients.

Current HBV treatments - Conclusions

- PEG-IFN for few patients, effective in some
- ETV/TDF for most CHB patients, very effective (>95%)
- IFN-NUC for selected patients, TAF available in 2017
- Prevention of clinical decompensation, improvement of portal hypertension, HCC the only complication
- Excellent 5-yr overall and liver-related survival
- New strategies/drugs needed to reduce HCC (?) and to improve HBsAg loss rates