HBeAg-negative chronic hepatitis B
Why do I treat my patient with a nucleos(t)ide analogue?

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Conflict of Interest Statement

I use PegIFNα-2a in CHB
Estimated proportions of 1st line therapy in CHB patients in European countries

70-90% vs 10-30%
HBV-RELATED CHRONIC LIVER DISEASE
THERAPEUTIC INDICATIONS

NA(s) or (Peg-)IFNa

• Chronic hepatitis B

Only NA(s)

• Decompensated HBV cirrhosis
• Prophylaxis in HBV transplant cases
• Pre-emptive therapy in inactive HBV carriers receiving immunosuppressive/chemo-therapy
• Pregnant women with high HBV viremia
• Health care workers in the HBV immunotolerant phase
TREATMENT OPTIONS IN HBeAg(-) CHB NA(s) vs Peg-IFNa
Patients prefer pills than injections

One pill per day!
NAs: much better tolerability and safety compared to (Peg-)IFNa
### Safety (Renal) monitoring during NA therapy

- Assess baseline creatinine clearance (Clcr) regardless of NA

<table>
<thead>
<tr>
<th>Renal risk</th>
<th>Antiviral</th>
<th>Test (C1)</th>
<th>Frequency (C2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>ADV, TDF</td>
<td>Clcr,</td>
<td>0, 3, 6, 9, 12 &amp; then every 6 months</td>
</tr>
<tr>
<td>High</td>
<td>ADV, TDF</td>
<td>phosphate</td>
<td>0, 1, 2, 3, 6, 9, 12 &amp; then every 6 months</td>
</tr>
<tr>
<td></td>
<td>LAM, ETV, TBV</td>
<td>Clcr</td>
<td></td>
</tr>
</tbody>
</table>

**Peg-IFNa therapy:** FBC, ALT monthly & TSH every 3 months

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EASL HBV CPGs. J Hepatol 2012;57:167-85
**Safety during 288 weeks of TDF therapy**  
**Studies 0102 & 0103**

<table>
<thead>
<tr>
<th>Event</th>
<th>Total TDF (OL Period) (N=585)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events leading to drug discontinuation</td>
<td>11 (1.9%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Serious adverse events*</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse events*</td>
<td>6 (1.0%)</td>
</tr>
<tr>
<td>Confirmed Scr ≥0.5 mg/dL above baseline</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Confirmed PO₄ &lt;2 mg/dL</td>
<td>8 (1.4%)</td>
</tr>
<tr>
<td>Confirmed CrCL &lt;50 mL/min (Cockcroft–Gault method)</td>
<td>6 (1.0%)</td>
</tr>
</tbody>
</table>

*Study drug-related adverse events only

Marcellin P et al. AASLD 2012
eGFR changes in CHB pts under TBV or LAM for 2 yrs

Gane E et al. EASL 2012

<table>
<thead>
<tr>
<th>% change from baseline in GFR</th>
<th>TBV</th>
<th>LAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>8.5</td>
<td>17.2</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>11.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Baseline GFR 60-90 ml/min</td>
<td>-0.5</td>
<td>-2.4</td>
</tr>
</tbody>
</table>

N=680  N=687               N=87   N=100              N=256  N=234
TREATMENT OPTIONS IN HBeAg(-) CHB NA(s) vs (Peg-)IFNa

Efficacy
### Virological responses at 1 year in HBeAg-negative CHB

**HBV DNA drop**

<table>
<thead>
<tr>
<th>Log$_{10}$ cp/mL</th>
<th>Peg-IFNa-2a</th>
<th>LAM</th>
<th>ADV</th>
<th>ETV</th>
<th>TBV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4.1</td>
<td>63%</td>
<td>70%</td>
<td>63%</td>
<td>90%</td>
<td>88%</td>
<td>93%</td>
</tr>
<tr>
<td>-4.4/-4.5</td>
<td>65%</td>
<td></td>
<td>51%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-3.9/-4.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-5.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-5.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-4.5</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Patients with undetectable serum HBV DNA at 48-52 wks, %**

- Peg-IFNa-2a: 63%
- LAM: 70%
- ADV: 63%
- ETV: 90%
- TBV: 88%
- TDF: 93%

**HBV DNA, cp/mL**

- <400
- <300
- <400
- <300
- <300
- <400

**References**

- Marcellin 2004
- Tassopoulos 1999
- Papatheodoridis 2002
- Hadziyannis 2003
- Lai 2006
- Lai 2007
- Marcellin 2008
Efficacy of 12-Month Courses in HBeAg(-) CHB: Sustained off-therapy responses

Biochemical & virological responses (different definitions among studies)

- **End of therapy**
- **Sustained**

<table>
<thead>
<tr>
<th>Medication</th>
<th>End of therapy</th>
<th>Sustained</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNa (3MU tiw) x12 mos</td>
<td>54%</td>
<td>22%</td>
</tr>
<tr>
<td>Peg-IFNa (180 μg/wk x12 mos)</td>
<td>36%</td>
<td>25%</td>
</tr>
<tr>
<td>LAM (100 mg/d x12 mos)</td>
<td>70%</td>
<td>&lt;11%</td>
</tr>
<tr>
<td>ADV (10 mg/d x12 mos)</td>
<td>74%</td>
<td>8%</td>
</tr>
<tr>
<td>ETV (0.5 mg/d x12 mos)</td>
<td>78%</td>
<td>2%</td>
</tr>
<tr>
<td>TBV (600 mg/d x12 mos)</td>
<td>74%</td>
<td>7%</td>
</tr>
<tr>
<td>TDF (300 mg/d x12 mos)</td>
<td>77%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Efficacy of current treatment options in HBeAg(-) CHB

- 12-month courses of Peg-IFNa better sustained off-treatment response rates than 12-month courses of NA(s)

- Peg-IFNa: responses in a minority of patients
  - NA(s): high on-treatment remission rates
  - NA(s) duration: >4-5 years, indefinitely?

- Viral resistance?
Resistance to oral antiviral agents in naive CHB patients

Data from different studies with different patients characteristics and methodology

Long-term therapy with ETV/TDF in HBeAg(-) CHB

• **Viral resistance:**
  not an issue in clinical practice in 2013

• **Virological response rates:**
  >90% at year-1, >98% after year-2

• **Absence of virological response under ETV or TDF:**
  check for drug compliance
Partial virological response under ETV/TDF

Check for compliance

In compliant patients with partial virological response under

- 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)

EASL HBV CPGs. J Hepatol 2012;57:167-85
• Serum HBV DNA at 3 and then every 3-6 months

• During ETV or TDF therapy, the frequency of HBV DNA follow-up may be decreased when patient compliance and treatment efficacy have been established (C1)

EASL HBV CPGs. J Hepatol 2012;57:167-85
Long-term therapy with NA(s) in HBeAg(-) CHB

Effects on major outcomes including survival
Fibrosis Is Reversible
Liver Fibrosis Regression over 5 Years of TDF Therapy

348 patients with paired biopsies at baseline & year 5

- Patients with cirrhosis (Ishak score ≥5): 28% at baseline, 8% at year 5

Disease progression in patients with HBeAg(+)/(−) HBV cirrhosis under long-term LAM monotherapy

Liaw YF et al. NEJM 2004
Major event free survival under LAM ± salvage ADV

Log-rank test

Pts in virologic remission

Pts with virologic no response or VBTHs

Follow-up (months)

HCC in CHB patients under LAM

- LAM treated pts
  - All: 2.8%
  - VR: 2.5%
  - BR/BTH: 2.8%
  - Untreated pts: 6.4%

- LAM:
  - Patients: 779
  - HBeAg(-): 49%
  - Comp. Ci: 29%
  - FUP (mos): 32-90

- Untreated:
  - Patients: 534
  - HBeAg(-): 54%
  - Comp. Ci: 39%
  - FUP (mos): 32-108

- P values:
  - Patients n: P=0.003
  - HBeAg(-): P=0.015
  - Comp. Ci: P=0.016

- References:
  - Liaw et al, NEJM 2004
  - Papatheodoridis et al, HEP 2005
  - Yuen et al, AVT 2007

Papatheodoridis, Lampertico, Manolakopoulos, Lok. J Hepatol 2010;53:348-56
HCC in patients with HBV cirrhosis under NA(s) starting with LAM

P = 0.327

Papatheodoridis GV et al. Gut 2011, 60: 1109-16
HCC incidence in patients with HBV cirrhosis treated with entecavir

HCC=17
HCC rate/year: 2.8%

Lampertico P et al. AASLD 2012
HCC incidence in patients with CHB treated with entecavir

Hosaka T et al. Hepatology 2012 Dec 5 [Epub ahead of print]
LONG-TERM ORAL ANTIVIRAL THERAPY IN HBeAg(-) CHB

• Can we ever stop?
Long-term NA therapy in HBeAg-negative CHB

- **Safe discontinuation:** HBsAg loss
  - HBsAg loss: 0-1% at 4-5 years
  - **APASL:** stop NA if HBV DNA (-) on 3 6-monthly occasions

- NA discontinuation in non-cirrhotic HBeAg(-)CHB patients in virological remission under 4-5 years ADV therapy

Sustained off-therapy response: ~35% (f-up ≥5 yrs)

Hadziyannis SJ et al. Gastroenterology 2012;143:629-636
HBsAg loss in patients with HBeAg(-) CHB who remained in virological remission under ADV for 4-5 years

HBsAg levels at EOT: independent predictor of sustained off-treatment response and HBsAg loss

Hadziyannis SJ et al. Gastroenterology 2012;143:629-636
HBsAg levels as a marker for safe discontinuation of NA therapy in CHB

- HBsAg at end of NAs <100 IU/mL

- 81 (50 e+, 31 e-) pts with post-NAs f-up 32±24 months

  HBsAg at end of NAs <100 IU/mL - AUROC for SVR: 99%
  (sens: 100%, spec: 93%, PPV: 69%, NPV: 100%)

  Suh SJ et al. EASL 2012

- 77 (38 e+, 39 e-) pts with post-NAs f-up ≥6 months

  12-month relapse rates in relation to HBsAg at end of NAs -
  <100 IU/mL: 0%, 100-1000 IU/mL: 50%, >1000 IU/mL: 78%

  Jiang JN et al. EASL 2012
Towards finite treatment duration

- NA(s) discontinuation after a certain duration
- NA(s) discontinuation in patients with favorable markers of sustained off-therapy remission (e.g., low HBsAg levels)
- Peg-IFN after some years of NA therapy
- Peg-IFNa/λ + ETV or Peg-IFNa + TDF
- TLR7 agonists + ?
HBeAg-negative chronic hepatitis B
Why do and shall I treat my patients with a NA?

• No contraindication
• Excellent tolerability & good safety
• On-treatment responses in almost all patients
• Minimal safety & efficacy monitoring
• Improved histology & long-term outcomes
• Patients’ preference (one pill per day)
• Even in majority of PegIFNa treated patients–PegFNa failures
• Cost reduction in the future (already very cheap in some developing countries)
• Probably part of any future combination
Thank you