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

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Estimated proportions of 1\textsuperscript{st} line therapy in CHB patients in European countries

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

THERAPEUTIC INDICATIONS

NUC(s) or (Peg-)IFNa
• Chronic hepatitis B

Only NUC(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

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TREATMENT OPTIONS IN CHB
NUC(s) vs (Peg-)IFNa
3 nucleoside analogues

3 nucleoside analogues

2 nucleotide analogues

peg-IFNa-2a

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TREATMENT OPTIONS IN HBeAg(-) CHB
NUC(s) vs (Peg-)IFNa

Efficacy
Therapeutic aims in CHB

- Inhibition of CHB progression
- Change of CHB into inactive carrier state
- Prevention of cirrhosis
- Prevention of HBV eradication
- Virological & biochemical remission
- Improvement of survival
- Prevention of HCC
Virological responses at 1 year in HBeAg-negative CHB

- HBV DNA drop
  - log_{10} cp/mL
  - -4.1
  - -4.4/-4.5
  - -3.9/-4.1
  - -5.0
  - -5.2
  - -4.5

- Patients with undetectable serum HBV DNA at 48-52 wks, %
  - 63%
  - 70%
  - 63%
  - 90%
  - 88%
  - 93%

- HBV DNA, cp/mL
  - <400
  - <300
  - <400
  - <300
  - <300
  - <400

- Marcellin 2004
  - Tassopoulos 1999
  - Hadziyannis 2003
  - Lai 2006
  - Marcellin 2008
  - Lai 2007
  - Marcellin 2008

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EFFICACY OF 12-MONTH COURSES IN HBeAg(-) CHB: Sustained off-therapy responses

Biochemical & virological responses (different definitions among studies)

<table>
<thead>
<tr>
<th>Drug</th>
<th>IFNa</th>
<th>Peg-IFNa</th>
<th>LAM</th>
<th>ADV</th>
<th>ETV</th>
<th>TBV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of therapy</td>
<td>54%</td>
<td>36%</td>
<td>70%</td>
<td>74%</td>
<td>78%</td>
<td>74%</td>
<td>77%</td>
</tr>
<tr>
<td>Sustained</td>
<td>22%</td>
<td>25%</td>
<td>&lt;11%</td>
<td>8%</td>
<td>2%</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

- **IFNa**: 3MU tiw x12 mos
- **Peg-IFNa**: 180 μg/wk x12 mos
- **LAM**: 100 mg/d x12 mos
- **ADV**: 10 mg/d x12 mos
- **ETV**: 0.5 mg/d x12 mos
- **TBV**: 600 mg/d x12 mos
- **TDF**: 300 mg/d x12 mos

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EFFICACY OF 12-MONTH COURSES IN HBeAg(-) CHB: Sustained off-therapy responses

- 12-month courses of Peg-IFNa better than 12-month courses of NUC(s)
  - Peg-IFNa: responses in a minority of patients
  - NUC(s) therapy: >4-5 years, indefinitely?
Resistance to oral antiviral agents in naive HBeAg(-)CHB

Data from different studies with different patients characteristics and methodology


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Long-term ETV (re)treatment in HBeAg(-) CHB

Patients with με HBV DNA <300 cp/mL (%)

ETV-027

94

ETV-901

83 93 94 91 98

D

NA <30

4 20 30

EOD

94/99 56/95 79/95 84/90 72/77 67/74 54/57

Wk

12 24 48 72 96 144

n=

93/99 4/99 59 72/77 67/74 54/57

Patien

t

Shouval et al. Hepatology 2008; 48: 722A HBsAg loss: 0%

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Study 102 - HBeAg-Negative Patients

Virological Response: HBV DNA <400 cp/mL

- **ITT: LTE-TDF Analysis**
  - TDF-TDF
  - ADV-TDF

- **On-Treatment Analysis**

Marcellin P et al. AASLD 2010, Poster #476
Long-term therapy with ETV/TDF in HBeAg(-) CHB

- **Viral resistance:**
  not an issue in clinical practice in 2011

- **Absence of virological response under ETV or TDF:**
  check for drug compliance
<table>
<thead>
<tr>
<th>Resistance</th>
<th>Rescue therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM-R</td>
<td>Add TDF (or ADV if TDF is not available)</td>
</tr>
<tr>
<td>LdT-R</td>
<td>Add TDF (or ADV if TDF is not available)</td>
</tr>
<tr>
<td>ETV-R</td>
<td>Add TDF</td>
</tr>
</tbody>
</table>
| ADV-R      | N236T: Add LAM or LdT or switch to TDF/FTC  
            | A181T/V: Add ETV or switch to TDF/FTC      |
| TDF-R      | Add ETV, LdT, LAM or FTC               |

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Long-term therapy with NUC(s) in HBeAg(-) CHB

Effects on major outcomes including survival
Survival in IFNα-Treated Patients with HBeAg(-)CHB

Proportion of pts surviving

- IFNα treated: sustained response
- IFNα treated: no sustained response

Proportion of pts free of major complications

- Untreated

SR in only 20-25% of patients

Years

2 4 6 8 10 12 14

P=0.027 SR vs non-SR
P=0.048 SR vs untreated

P=0.019 SR vs non-SR
P=0.012 SR vs untreated

Papatheodoridis et al. J Hepatol 2001; 34: 306-313

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Changes of necroinflammation in HBeAg(-)CHB under long-term lamivudine monotherapy

- **Change of grading score of ≥2 points (Ishak* - HAf#)**

<table>
<thead>
<tr>
<th>Group</th>
<th>No YMDD (n=12)</th>
<th>YMDD+ (n=16)</th>
<th>No YMDD (n=22)</th>
<th>YMDD+ (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of 2nd Bx:</td>
<td>26 mos</td>
<td>24 mos</td>
<td>after LAM onset</td>
<td></td>
</tr>
</tbody>
</table>

- **P=0.02**
- **P=0.001**

*Papatheodoridis et al, Hepatology 2002; 36: 219-26

#Rizzetto et al, J Hepatol 2005; 42: 173-9
Changes of fibrosis in HBeAg(-)CHB under long-term lamivudine monotherapy

Change of fibrosis score of ≥1 point (Ishak)

<table>
<thead>
<tr>
<th></th>
<th>No YMDD (n=12)</th>
<th>YMDD+ (n=16)</th>
<th>No YMDD (n=22)</th>
<th>YMDD+ (n=26)</th>
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</table>

Papatheodoridis et al, Hepatology 2002; 36: 219-26
Long-term entecavir monotherapy: Effect on necroinflammation

Necroinflammation
Knodell score

- 10–14
- 7–9
- 4–6
- 0–3
- Missing data

N=57

Baseline Week 48 5.4 (3-7) years

Chang TT et al. Hepatology 2010; 52: 886-93
Long-term entecavir monotherapy: Effect on fibrosis

Fibrosis Ishak score
- 6
- 5
- 4
- 3
- 2
- 1
- 0
- Missing data

N=57

Chang TT et al. Hepatology 2010; 52: 886-93
Disease progression in patients with HBeAg(+) /(-) HBV cirrhosis under long-term LAM monotherapy

Liaw et al, *NEJM* 2004
Major event free survival under LAM ± salvage ADV

Pts in virologic remission

Pts with virologic no response or VBTHs

Log-rank test

P=0.07

Follow-up (months)


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HCC in CHB patients under LAM

- **Patients n:** 779 (LAM) vs. 534 (Untreated)
- **HBeAg(-)**: 49% (LAM) vs. 54% (Untreated)
- **Comp. Ci:** 29% (LAM) vs. 39% (Untreated)
- **FUP (mos):** 32-90 (LAM) vs. 32-108 (Untreated)

- **Patients with HCC, %:**
  - All: 2.8 (LAM) vs. 2.8 (Untreated)
  - VR: 2.5 (LAM) vs. 2.8 (Untreated)
  - BR/BTH: 6.4 (Untreated)

- **P-values:**
  - 0.003
  - 0.015
  - 0.016

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

LONG-TERM ORAL ANTIVIRAL THERAPY IN HBeAg(-) CHB

• Can we ever stop?
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
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HBsAg loss in patients with HBeAg(-) CHB who remained in virological remission under ADV for 4-5 years

Hadziyannis SJ et al. EASL 2009, Abstr. 18

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HBsAg loss in patients with HBeAg(-) CHB treated with Peg-IFNa-2a or ADV


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LONG-TERM ORAL ANTIVIRAL THERAPY IN HBeAg(-) CHB

• Can newer, more potent NUCs (ETV/TDF) offer higher sustained off-therapy response & HBsAg loss rates after long-term virological remission?
CHRONIC HEPATITIS B
Which therapy for whom?

IFNa (Peg-IFNa-2a)
- Young (reproductive) age
- Favorable factors of response to IFNa (low HBV DNA, high ALT, genotype A vs D – not very well defined in HBeAg-neg. CHB)
- Patient’s preference

ETV/TDF
- Not candidates for IFNa
- No sustained response with IFNa
- Contraindication for IFNa
- Patient’s preference
## Main characteristics of patients with HBeAg(-) CHB

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients, n</strong></td>
<td>209</td>
<td>399</td>
<td>101</td>
<td>127</td>
<td>177</td>
</tr>
<tr>
<td><strong>Type of study</strong></td>
<td>IFNa RE cohort</td>
<td>Consecutive patients</td>
<td>IFNa PR cohort</td>
<td>Peg-IFNa-2a PR cohort</td>
<td>Peg-IFNa-2a PR cohort</td>
</tr>
<tr>
<td><strong>Origin</strong></td>
<td>Greeks</td>
<td>Greeks</td>
<td>Italians</td>
<td>Italians</td>
<td>Asians: 60%</td>
</tr>
<tr>
<td><strong>Age (years), mean±SD</strong></td>
<td>47±11</td>
<td>49±14</td>
<td>46±10</td>
<td>45</td>
<td>40±12</td>
</tr>
<tr>
<td><strong>Sex, M (%)</strong></td>
<td>83%</td>
<td>77%</td>
<td>87%</td>
<td>NA</td>
<td>85%</td>
</tr>
<tr>
<td><strong>ALT (IU/L), median</strong></td>
<td>67</td>
<td>99</td>
<td>mean±SD: 204±180</td>
<td>95</td>
<td>62</td>
</tr>
<tr>
<td><strong>Median HBV DNA</strong></td>
<td>4.8 pg/mL</td>
<td>6.3 log&lt;sub&gt;10&lt;/sub&gt; IU/ml</td>
<td>NA</td>
<td>6 log&lt;sub&gt;10&lt;/sub&gt; IU/ml</td>
<td>7 log&lt;sub&gt;10&lt;/sub&gt; cp/ml</td>
</tr>
</tbody>
</table>

RE: retrospective, PR: prospective, NA: not available

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**HBeAg-negative chronic hepatitis B**

Why do I treat my chronic hepatitis B patients with a nucleos(t)ide analogue?

- No contraindication
- Better Tolerability & Safety
- On-treatment responses in almost all patients
- Improved histology with reversion of fibrosis
- Improved long-term outcomes incl. reduction in HCC
- Patients’ preference
- NUC(s) even in the majority of IFNa treated patients – IFNa failures

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