HBeAg-negative chronic hepatitis B
Why do I treat my patients with pegylated interferon-alfa?

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

Conflict of Interest Statement

I use PegIFNα-2a in CHB
HBV-RELATED CHRONIC LIVER DISEASE
THERAPEUTIC INDICATIONS

**PegIFNa or NA(s)**
- Chronic hepatitis B (including compensated cirrhosis)

**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
PegIFNa vs NA(s)
Virological responses at 1 year in HBeAg-negative CHB

<table>
<thead>
<tr>
<th>HBV DNA drop $\log_{10}$ cp/mL</th>
<th>PegIFNa-2a</th>
<th>LAM</th>
<th>ADV</th>
<th>ETV</th>
<th>TBV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
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<tr>
<td>-4.1</td>
<td>63%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>-4.4/-4.5</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-3.9/-4.1</td>
<td>63%</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>-5.0</td>
<td>90%</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>-5.2</td>
<td>88%</td>
<td></td>
<td></td>
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<tr>
<td>-4.5</td>
<td>93%</td>
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</tr>
</tbody>
</table>

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

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

HBV DNA, cp/mL

- <400 Marcellin 2004
- <400 Hadziyannis 2003
- <300 Lai 2006
- <300 Lai 2007
- <400 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 off-therapy**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>End of Therapy</th>
<th>Sustained off-therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNa</td>
<td>54%</td>
<td>22%</td>
</tr>
<tr>
<td>PegIFNa</td>
<td>36%</td>
<td>23%</td>
</tr>
<tr>
<td>LAM</td>
<td>&lt;11%</td>
<td>8%</td>
</tr>
<tr>
<td>ADV</td>
<td>74%</td>
<td>2%</td>
</tr>
<tr>
<td>ETV</td>
<td>78%</td>
<td>?%</td>
</tr>
<tr>
<td>TBV</td>
<td>74%</td>
<td>?%</td>
</tr>
<tr>
<td>TDF</td>
<td>77%</td>
<td>?%</td>
</tr>
</tbody>
</table>

- **3MU tiw**
- **180 μg/wk**
- **100 mg/d**
- **10 mg/d**
- **0.5 mg/d**
- **600 mg/d**
- **300 mg/d**

- **x12 mos**

- **Manesis 2001**
- **Marcellin 2004, 2013**
- **Tassopoulos 1999**
- **Hadziyannis 2005**
- **Shouval 2004/2006**
- **Lai 2005**
- **Marcellin 2007**
PegIFNa-2a achieves durable sustained off-treatment response (immune control) in HBeAg-neg. CHB

230 patients with HBeAg-negative CHB treated with PegIFNa-2a ± LAM

HBsAg clearance rates continue to increase after the end of IFNa/Peg-IFNa-2a treatment in HBeAg-neg. sustained responders

Mainly Gen. D

Marcellin et al. Hepatol Int 2013

All patients
N=230

Gen. D n=47

Patients at Risk

Years after end of IFNa

Years after end of Peg-IFNa-2a

Manesis & Hadziyannis. Gastroenterology 2001
Survival in IFNa-Treated Patients with HBeAg(-)CHB

Proportion of pts surviving

Proportion of pts free of major complications

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

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

IFNa treated: sustained response

IFNa treated: no sustained response

Untreated
EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

The main theoretical advantages of (PEG-)IFN are the absence of resistance and the potential for immune-mediated control of HBV infection with an opportunity to obtain a sustained virological response off-treatment and a chance of HBsAg loss in patients HBeAg-negative patients, as it is practically the only option that may offer a chance for sustained off-treatment response after a finite duration of therapy.
Optimisation of PegIFNa therapy in HBeAg-negative CHB

- Longer PegIFNa courses?
- Combination of PegIFNa with newer NAs (ETV or TDF)?
- Prediction of PegIFNa response or no response
  - Baseline
  - Early on-therapy
24-month IFNa therapy in HBeAg-neg. CHB

101 patients: IFNa-2b 6MU x3/wk x24 months

- Sustained off-treatment response: 30%
- HBsAg loss: 15%

[ALT<ULN & HBV DNA (-) by non-PCR assays]

96-week PegIFNa therapy increases SVR rates in HBeAg-neg. CHB

PegIFNa-2a
- x48 wks (180μg/wk x48 wks), n=51
- x96 wks (180μg/wk x48 wks - 135μg/wk x48 wks), n=52

Patients with HBV DNA <2000 IU/mL, %

End-of-therapy
- 59

SR (48-wks post-therapy)
- 12

P=0.37

P=0.03

Excellent correlation between Elecsys (Roche) and Architecht (Abbott) over scale of 5 logs

Correlation between HBsAg levels measured by Elecsys vs Abbott

$y = 0.6052x^{1.0456}$

$R^2 = 0.9718$
Change in HBsAg levels: IFNa responders vs. LAM responders

- Rate of HBsAg decline was significantly higher in IFNa-treated compared to LAM-treated patients ($p=0.022$)
  - IFNa responders: median 155 IU/month
  - LAM responders: median 7.7 IU/month

- Median estimated time to HBsAg undetectability
  - IFNa 65.3 (36.3–95.0) months
  - LAM 127 (87.6–263.5) months

Manesis et al. Antivir Ther 2007
HBsAg decline with Peg-IFNa-2a can distinguish between relapsers and responders with HBeAg-neg. CHB

Sustained responders* (N=12)  
Relapsers** (N=18)  
Non-responders (N=18)

* HBV DNA undetectable by PCR 1 year post-treatment  
** HBV DNA undetectable at EOT but detected in following 24 weeks

Moucari et al. Hepatology 2009
Early serum HBsAg drop as a predictor of SVR in Peg-IFNa-2a treated CHBe- patients

<table>
<thead>
<tr>
<th>Week of Treatment</th>
<th>Sustained Virological Response</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12(^{th})</td>
<td>HBsAg Decrease: &gt;0.5 (\log_{10})</td>
<td>89%</td>
<td>90%</td>
</tr>
<tr>
<td>24(^{th})</td>
<td>HBsAg Decrease: &gt;1.0 (\log_{10})</td>
<td>92%</td>
<td>97%</td>
</tr>
</tbody>
</table>

SVR is defined as undetectable serum HBV DNA (<70 cp/mL) at 24 weeks after Rx

Moucari et al. Hepatology 2009
HBsAg decline is significantly associated with sustained immune control (1 year post-treatment)

230 patients with HBeAg-negative CHB treated with PegIFNa-2a ± LAM*

Week 12

P=0.0003

<table>
<thead>
<tr>
<th>HBV DNA ≤2,000 IU/mL</th>
<th>1 year post-treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10%</td>
<td>47%</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Week 24

P=0.0004

<table>
<thead>
<tr>
<th>HBV DNA ≤10,000 copies/mL</th>
<th>1 year post-treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10%</td>
<td>43%</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Marcellin et al. Hepatol Int 2013
HBsAg decline is significantly associated with sustained immune control (5 years post-treatment)

230 patients with HBeAg-negative CHB treated with PegIFNa-2a ± LAM*

Week 12

P=0.0005

Week 24

P=0.0002

Marcellin et al. Hepatol Int 2013
Peg-IFNa-2a in HBeAg(-)CHB: PARC rule
Pooled analysis of data from PARC, Phase III & PegBeLiver trials

Genotype D 172 (66%)

WEEK 12

262 patients

ANY HBsAg decline

No
N=138 (53%)

Yes
N=124 (47%)

HBV DNA decline (copies/mL)

<2 log
N=42 (30%)

≥2 log
N=96 (70%)

<2 log
N=42 (34%)

≥2 log
N=82 (66%)

Chance of sustained response*

1/42 (2%)

32/96 (33%)

15/42 (36%)

34/82 (41%)

16% (42/262)

*HBV DNA ≤10,000 cp/mL & ALT <ULN at 6 months post-therapy

Rijckborst et al. J Hepatol 2012;56:1006-11
Peg-IFNa stopping rules

• **HBeAg-ve (genotype D):** no decline in **HBsAg levels** and no **HBV DNA drop ≥2 log_{10} IU/mL by month 3** (B2)

EASL HBV CPGs. J Hepatol 2012
PERSEAS cohort: Validation of PARC rule

Peg-IFNa-2a (180 μg/wk x48wks)

Any HBsAg decline

<table>
<thead>
<tr>
<th>Week 12</th>
<th>47 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>No: 28/47 (60%)</td>
<td>Yes: 19/47 (40%)</td>
</tr>
</tbody>
</table>

HBV DNA decline >2 log\(_{10}\)

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
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<tbody>
<tr>
<td>8/47</td>
<td>20/47</td>
</tr>
</tbody>
</table>

SR*

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4/20 (25%)</td>
</tr>
<tr>
<td></td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td></td>
<td>7/14 (50%)</td>
</tr>
</tbody>
</table>

NPV: 100%

17% (8/47)

83% (39/47 pts)

*SR: HBV DNA <2,000 IU/mL at 48 wks post-therapy

Goulis et al. AASLD 2013
** PegBeLiver rule (week 24) **

47 pts treated for 48 wks – 8 pts excluded due to PARC stopping rule at week 12

<table>
<thead>
<tr>
<th>Week 24</th>
<th>39 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg ≤7500 IU/mL</td>
<td>15/39 (38%)</td>
</tr>
<tr>
<td>SR*</td>
<td>1/15 (7%)</td>
</tr>
</tbody>
</table>

- No
  - 15/39 (38%)
- Yes
  - 24/39 (62%)

**NPV: 93%**

8 + 15 = 22/47 (47%)

*SR: HBV DNA <2,000 IU/mL at 48 wks post-therapy

Lampertico et al. EASL 2012
### PERSEAS rule (week 24)

47 pts treated for 48 wks – 8 pts excluded due to PARC stopping rule at week 12

<table>
<thead>
<tr>
<th>Week 24</th>
<th>39 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBsAg decline &gt;10%</strong></td>
<td><strong>No</strong> 15/39 (38%)</td>
</tr>
<tr>
<td><strong>SR</strong></td>
<td>1/15 (7%)</td>
</tr>
<tr>
<td><strong>NPV: 93%</strong></td>
<td><strong>8+15=22/47 (47%)</strong></td>
</tr>
</tbody>
</table>

*SR: HBV DNA <2,000 IU/mL at 48 wks post-therapy

Goulis et al. AASLD 2013
TREATMENT OPTIONS IN HBeAg(-) CHB
PegIFNa vs NA(s)

Cost-effectiveness
PegIFNa-2a as first-line therapy in HBeAg(-)CHB using the 12-week HBV DNA/HBsAg stopping rule

- Decision analytic Markov model – lifetime simulation horizon
- 4 simulated strategies:
  1. NAs (ETV/TDF) as first-line therapy in CHB
  2. NAs (ETV/TDF) as first-line therapy delayed until compensated cirrhosis (CCi)
  3. PegIFN alfa-2a (Pegasys) as first-line therapy followed by ETV/TDF for patients meeting the week-12 stopping rule or for week-48 non-responders/relapsers
  4. PegIFN alfa-2a (Pegasys) as first-line therapy followed by ETV/TDF delayed until CCi
Cost-effectiveness comparisons (Discounted cost in euros)

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>ICER (Euros per QALY gained)</th>
</tr>
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<tbody>
<tr>
<td><strong>PegIFNa-2a as first-line therapy</strong></td>
<td></td>
</tr>
<tr>
<td>PegIFN+TDF in CHB (59,553) vs TDF in CHB (68,926)</td>
<td>Dominant</td>
</tr>
<tr>
<td>PegIFN+TDF in CCi (35,017) vs TDF in CCi (33,521)</td>
<td>1,152</td>
</tr>
<tr>
<td>PegIFN+ETV in CHB (85,228) vs ETV in CHB (103,897)</td>
<td>Dominant</td>
</tr>
<tr>
<td>PegIFN+ETV in CCi (42,764) vs ETV in CCi (43,454)</td>
<td>Dominant</td>
</tr>
<tr>
<td><strong>Early vs Delayed therapy with NAs</strong></td>
<td></td>
</tr>
<tr>
<td>TDF in CHB vs TDF in CCi</td>
<td>11,797</td>
</tr>
<tr>
<td>PegIFN+TDF in CHB vs PegIFN+TDF in CCi</td>
<td>12,118</td>
</tr>
<tr>
<td>ETV in CHB vs ETV in CCi</td>
<td>20,222</td>
</tr>
<tr>
<td>PegIFN+ETV in CHB vs PegIFN+ETV in CCi</td>
<td>20,778</td>
</tr>
</tbody>
</table>

S Iannazzo et al. Antiviral Therapy 2014, in press
1.5.8 Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications. [This recommendation is from Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96).]

1.5.16 Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-positive chronic hepatitis B and compensated liver disease.

1.5.18 Offer tenofovir disoproxil as second-line treatment.

1.5.19 Offer entecavir as an alternative second-line treatment.

1.5.23 Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-negative chronic hepatitis B and compensated liver disease.

1.5.25 Offer entecavir or tenofovir disoproxil as second-line treatment.
Peg-IFNa-2a has been shown to be cost-effective when compared to a number of similar treatments in a range of patient groups.
HBeAg-negative chronic hepatitis B
Why do I treat my patients with pegylated interferon-alfa?

• The best & practically the only chance for finite treatment duration achieving sustained immune control and even HBsAg loss, the closest outcome to a clinical cure

• Satisfactory on-therapy predictors of response & acceptable stopping rules

• Cost-effective approach
Thank you