WHAT IS THE ROLE OF INTERFERON IN 2012?

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TREATMENT OF CHRONIC HEPATITIS B
TWO STRATEGIES

• PEG IFN: Antiviral + immunomodulator

• NUCs: Pure antiviral
<table>
<thead>
<tr>
<th></th>
<th>NUCs</th>
<th>IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finite duration</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Sustained response</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>No resistance</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Oral administration</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Good tolerance</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>
PEG-IFN alpha 2a in HBeAg-positive patients

Lau et al. NEJM 2005
STUDY DESIGN

814 patients with HBeAg-positive CHB were randomized to receive lamivudine 100 mg qd, PEG-IFN a2a 180 µg qw + lamivudine 100 mg qd, or PEG-IFN a2a 180 µg qw + oral placebo qd.

Randomised

PEG-IFN a2a 180 µg qw + oral placebo qd

PEG-IFN a2a 180 µg qw + lamivudine 100 mg qd

lamivudine 100 mg qd

EOT 48 weeks

24 weeks post-treatment

Weeks

0 24 48 72

Lau et al. NEJM 2005
### BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>PEG-IFN a2a + placebo (n=271)</th>
<th>PEG-IFN a2a + lamivudine (n=271)</th>
<th>lamivudine (n=272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>79%</td>
<td>77%</td>
<td>79%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>9%</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Asian (%)</td>
<td>87%</td>
<td>87%</td>
<td>85%</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>66</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>Mean baseline ALT (x ULN)</td>
<td>3.8</td>
<td>3.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Mean baseline HBV DNA (log_{10} cp/mL)</td>
<td>9.7</td>
<td>10.1</td>
<td>10.1</td>
</tr>
<tr>
<td>Bridging fibrosis/cirrhosis (%)</td>
<td>18%</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>Prior use of lamivudine (%)</td>
<td>12%</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Prior use of conventional IFNα (%)</td>
<td>11%</td>
<td>12%</td>
<td>12%</td>
</tr>
</tbody>
</table>
HBV DNA < 400 copies/mL

PEG IFN a2a + placebo
PEG IFN a2a + Lamivudine
Lamivudine
PEG IFN a2a + placebo + Lamivudine
PEG IFN a2a + Lamivudine
Lamivudine

HBV DNA response (%)

EOT

24 weeks Post-treatment

P<0.001

25%

69%

40%

14%

14%

5%
HBeAg SEROCONVERSION

HBV DNA response (%)

- PEG IFN a2a + placebo: 27%
- PEG IFN a2a + Lamivudine: 24%
- Lamivudine: 20%
- PEG IFN a2a + placebo: 32%
- PEG IFN a2a + Lamivudine: 27%
- Lamivudine: 19%

EOT (24 weeks) vs. Post-treatment
HBsAg LOSS AND SEROCONVERSION

24 weeks post-treatment

3% 4% <1%
PEG-IFN alpha 2a in HBeAg-negative patients

Marcellin et al. NEJM 2004
537 patients with HBeAg-negative CHB were randomized to receive:

- Lamivudine 100 mg qd
- PEG-IFN a2a 180 µg qw + lamivudine 100 mg qd
- PEG-IFN a2a 180 µg qw + oral placebo qd

Weeks:
- Randomised: 0
- EOT: 48 weeks
- 24 weeks post-treatment: 72

Marcellin et al. NEJM 2004
## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>PEG-IFN a2a + placebo (n=177)</th>
<th>PEG-IFN a2a + lamivudine (n=179)</th>
<th>Lamivudine (n=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>85%</td>
<td>82%</td>
<td>86%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>37%</td>
<td>36%</td>
<td>38%</td>
</tr>
<tr>
<td>Asian (%)</td>
<td>60%</td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>40</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>71</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>Mean ALT (x ULN)</td>
<td>3.1</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Mean HBV DNA (log_{10} copies/ml)</td>
<td>7.14</td>
<td>7.35</td>
<td>7.24</td>
</tr>
<tr>
<td>Bridging fibrosis/cirrhosis (%)</td>
<td>31%</td>
<td>22%</td>
<td>29%</td>
</tr>
<tr>
<td>Prior use of lamivudine (%)</td>
<td>4%</td>
<td>8%</td>
<td>5%</td>
</tr>
</tbody>
</table>
HBV DNA < 400 copies/mL

HBV DNA response (%)

PEG IFN a2a + placebo
63%

PEG IFN a2a + Lamivudine
87%

Lamivudine
73%

PEG IFN a2a + placebo + Lamivudine
19%

PEG IFN a2a + Lamivudine
20%

Lamivudine
7%

EOT
24 weeks
Post-treatment
HBsAg LOSS AND SEROCONVERSION
24 weeks post-treatment

HBsAg loss

%
SAFETY
## ADVERSE EVENTS

<table>
<thead>
<tr>
<th></th>
<th>PEG-IFN a2a + placebo</th>
<th>PEG-IFN a2a + lamivudine</th>
<th>lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt with ≥1 adverse event</td>
<td>88%</td>
<td>87%</td>
<td>48%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>59%</td>
<td>55%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>42%</td>
<td>42%</td>
<td>18%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>27%</td>
<td>27%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>24%</td>
<td>19%</td>
<td>8%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18%</td>
<td>15%</td>
<td>3%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15%</td>
<td>15%</td>
<td>3%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>14%</td>
<td>11%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>6%</td>
<td>12%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Hepatic decompensation was not reported in any patient during the study.
### DEPRESSION

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN a2a + placebo</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>PEG-IFN a2a + lamivudine</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>lamivudine</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

- Depression rates are much lower than previously reported for PEG IFN in patients with chronic hepatitis C (16–20%).

Marcellin et al. Liver International 2008
PREDICTORS OF RESPONSE TO PEG IFN

- ALT > 3N
- HBV DNA < 6 log
- Liver necro-inflammatory
- Genotype A?
Qualitative HBsAg: Pronostic Marker for Disease Resolution

HBsAg loss close to a clinical cure

- Studies on natural history showed real clinical benefit:
  - Reduced hepatic decompensation
  - Reduced HCC
  - Improved survival

- Molecular studies
  - Extremely low levels of cccDNA in patients who cleared HBsAg
REVEAL study: Taiwan 1991–1992

Risk of HCC by HBV status

- **HBsAg+ HBeAg+**
  - RR 60.2

- **HBsAg+ HBeAg-**
  - RR 13.5

- **HBsAg-**
  - RR 1.0

Yang et al. NEJM 2002
HBsAg Clearance Improves Survival

Survival in patients with and without HBsAg seroconversion

Retrospective study of 309 *cirrhotic* patients over mean follow-up of 5.7 years

Fattovich et al. Am J Gastroenterol 1998
Low serum HBsAg levels correlate with low intrahepatic cccDNA.

We can use serum HBsAg as an indicator of the amount of cccDNA or number of infected cells in the liver?
Guidelines

HBsAg clearance is the “Ideal endpoint”

- AASLD, EASL and APASL guidelines all acknowledge the importance of HBsAg clearance
  - Key role in the natural history of chronic HBV infection

- EASL guidelines
  - “… is associated with a complete and definitive remission of the activity of CHB and an improved long-term outcome”
HBsAg CLEARANCE INCREASES OVER TIME AFTER RESPONSE TO IFN* (n = 100)

* HBe seroconversion

Responders: 64%
Non responders: 17%

Moucari et al. J Hepatol 2009

p < .001
HBsAg LOSS after PEG IFN ± LAM

Marcellin et al. NEJM 2004
Marcellin et al. Gastroenterology 2009
Marcellin et al. Hepatology International 2012
HBsAg LOSS

64% of the patients HBV DNA negative

Marcellin et al. NEJM 2004
Marcellin et al. Gastroenterology 2009
Marcellin et al. Hepatology International 2012
HBsAg ACCORDING TO TREATMENT:

Marcellin et al. Hepatology International 2012
Quantification of HBsAg: “Stopping Rule”
Early Serological Response = 0.5 log at W12

48 Patients treated with PEG IFN a2a

ESR + → PPV = 89%

ESR - → NPV = 90%

SVR
Sustained Virological response

Moucari et al. Hepatology 2009
SVR (HBV DNA < 2000 IU/mL) according to HBsAg decline during PEG IFN

- **HBsAg decline from BL to Week 12**
  - ≥10%: 47 (N=25)
  - <10%: 16 (N=11)
  - P=0.0005

- **HBsAg decline from BL to Week 24**
  - ≥10%: 43 (N=29)
  - <10%: 13 (N=7)
  - P=0.008

Marcellin et al. Hepatology International 2012
PEG IFN alpha 2a in HBeAg-positive: Dose and duration are important.

**NEPTUNE study**

- **N=136**
  - PEG IFN 180 µg
  - Follow-up

- **N=136**
  - PEG IFN 90 µg
  - Follow-up

- **N=136**
  - PEG IFN 180 µg
  - Follow-up

- **N=140**
  - PEG IFN 90 µg
  - Follow-up

Highest sustained response with 180 µg and 48 weeks confirms Phase 3 study.

Liaw et al. Hepatology 2011
NEPTUNE confirms association of on-treatment HBsAg level with HBe seroconversion.

**HBsAg at week 12 (IU/mL)**

- Low (<1500): 18/31 (58%)
- Medium (1500–20,000): 26/62 (42%)
- High (>20,000): 0/21 (0%)

**HBsAg at week 24 (IU/mL)**

- Low (<1500): 26/46 (57%)
- Medium (1500–20,000): 18/52 (35%)
- High (>20,000): 0/16 (0%)

Gane et al. EASL 2011
The S-Collate Cohort Study: interim analysis at week 48

- **HBV DNA <2000 IU/mL**: 90% (363/402)
- **ALT normalization**: 54% (290/535)
- **HBV DNA <2000 IU/mL + ALT normalization**: 49% (179/365)
- **HBsAg clearance**: 5% (26/491)

Marcellin et al. APASL 2012
HBsAg loss in patients with ≥10% vs <10% decline in HBsAg from baseline to weeks 12 and 24

Patients with HBsAg clearance at week 48 (%)

Week 12
- ≥10%: 12/99
- <10%: 2/102

Week 24
- ≥10%: 11/124
- <10%: 2/69

p=0.0051
p=0.1413

Marcellin et al. APASL 2012
Monitoring HBsAg Decline

PEG-IFN

Null responder

Slow responder

Rapid responder

Weeks

24 48 96

HBsAg level IU/mL

High

Low
THE ROLE OF

COMBINATION THERAPY WITH

PEG IFN + NUC
Potential benefits of combination therapy

- Achieve synergistic antiviral + immune effects
- Sustained loss of detectable HBV DNA
- Reduction in drug resistance
- Decrease cccDNA
- Increase HBsAg loss
CONCLUSION

- Finite duration treatment with PEG-IFN induces:
  - Inactive carrier state in 30-50%
  - SVR with undetectable HBV DNA in 15-25%
  - More rapid decline of HBsAg than NUCs
  - Loss of HBsAg in 10-15% at 5 years
CONCLUSION

- Loss of serum HBsAg:
  - The closest to clinical cure
  - The primary end-point in future trials

- Quantitative serum HBsAg:
  - Predicts Response to IFN-based treatment
  - May help to tailor treatment duration
CONCLUSION

The combination of PEG IFN with a potent NUC may accelerate HBsAg decline and improve HBsAg clearance rate.
The Future?
Individualised Therapy