Treatment of Chronic Hepatitis B with pegylated interferon

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Chronic Hepatitis B has Serious Long-term Consequences

- **HBeAg-positive CHB**
  - 15-20% develop cirrhosis in 5 yrs

- **HBeAg-negative CHB**

- **Cirrhosis**
  - Decompensation*

- **Hepatocellular carcinoma (HCC)**

- **Death**


Lok NEJM 2002
## Importance of serological clearance of HBsAg in reducing HCC

Study of HBV progression and HCC in 11,893 men in Taiwan

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBeAg</th>
<th>ALT</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
<td>--</td>
<td>normal</td>
<td>1 (23/71,105 person-yr)</td>
</tr>
<tr>
<td>--</td>
<td>--</td>
<td>elevated</td>
<td>5.4</td>
</tr>
<tr>
<td>+</td>
<td>--</td>
<td>normal</td>
<td>10.3</td>
</tr>
<tr>
<td>+</td>
<td>--</td>
<td>elevated</td>
<td>29.3</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>normal</td>
<td>61.3</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>elevated</td>
<td>109</td>
</tr>
</tbody>
</table>

Yang et al., NEJM 2002
# Registered treatment of HBeAg-Positive Chronic Hepatitis B (CHB) -2006

<table>
<thead>
<tr>
<th>Immune therapy (finite)</th>
<th>Anti-viral (life-long)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional IFN-α</td>
<td>Lamivudine</td>
</tr>
<tr>
<td><em>Pegylated IFN-α2a</em></td>
<td>Adefovir dipivoxil</td>
</tr>
<tr>
<td></td>
<td><em>Entecavir</em></td>
</tr>
</tbody>
</table>

- Immune control, no antiviral drugs
- Aim for sustained remission
- Continued need for antiviral drugs
- Suppression of viral replication
- ? Immune recovery
Pegylated Interferons

- Two pegylated interferons exist
  - Peginterferon alfa-2b (12KD)
  - Peginterferon alfa-2a (40KD) (PEGASYS®)
- They have different PEG moieties, which result in different pharmacokinetic profiles
# Peginterferon-α trials on HBeAg positive CHB

<table>
<thead>
<tr>
<th>Peg-IFN α2a</th>
<th>Peg-IFN α2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooksley 2003</td>
<td>Janssen 2005</td>
</tr>
<tr>
<td><strong>Comparator arm</strong></td>
<td><strong>LAM</strong></td>
</tr>
<tr>
<td>IFN</td>
<td>LAM</td>
</tr>
<tr>
<td>LAM</td>
<td></td>
</tr>
<tr>
<td>LAM+ pIFN</td>
<td></td>
</tr>
</tbody>
</table>

Hui et al Aliment Pharmacol Ther 2005
Investigator-initiated Peginterferon α-2b (12KD) Study Design

Patients with HBeAg-positive CHB were randomized using a 1:1 ratio

ITT population: n=266

- Peginterferon alfa-2b (12KD) 100 μg qw* + oral placebo
- Peginterferon alfa-2b (12KD) 100 μg qw* + lamivudine 100 mg od

Study weeks:

0 52 78

* PEG-IFNα-2b (12KD) dose reduced to 50 μg qw after 32 weeks

Janssen et al Lancet 2005
Peginterferon $\alpha$-2b ± Lamivudine
HBeAg Seroconversion

Patients (%)

End of Treatment
(Week 52)

PEG-IFN$\alpha$-2b + placebo
PEG-IFN$\alpha$-2b + lamivudine

22% 25% 29% 29%
n=136 n=130 n=136 n=130

P=0.52

P=0.92

End of Follow-up
(week 78)

Janssen et al. Lancet 2005
Peginterferon α-2b ± Lamivudine
HBV DNA < 200,000 copies/ml

Patients (%)

End of Treatment (Week 52)
- PEG-IFNα-2b + placebo: 29% (n=136)
- PEG-IFNα-2b + lamivudine: 74% (n=130)

End of Follow-up (week 78)
- PEG-IFNα-2b + placebo: 27% (n=136)
- PEG-IFNα-2b + lamivudine: 32% (n=130)

P<0.001
P=0.44

Janssen et al Lancet 2005
Lamivudine ± Peginterferon α-2b treatment in HBeAg-positive CHB

Log rank test
P=0.0015

<table>
<thead>
<tr>
<th>Post-treatment week</th>
<th>0</th>
<th>24</th>
<th>52</th>
<th>76</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combo (n=48)</td>
<td>63%</td>
<td>33%</td>
<td>31%</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>Lamivudine (n=47)</td>
<td>28%</td>
<td>13%</td>
<td>11%</td>
<td>9%</td>
<td>9%</td>
</tr>
</tbody>
</table>

SVR = sustained HBeAg seroconversion and HBV DNA <100,000 cp/ml

Chan HL et al Hepatology 2005
Pegasys on chronic HBV infection

• Phase II study
  – Proof-of-concept study (n= 194)
    » Cooksley et al J Viral Hepat 2003

• Phase III study
  – HBeAg negative (n=537)
    » Marcellin et al NEJM 2004
  – HBeAg positive (n=814)
    » Lau et al NEJM 2005
Peginterferon α-2a (40KD) in HBeAg-Positive Chronic Hepatitis B (CHB): a phase II study

194 IFN-naive randomised

EOT 24 weeks

24-week follow-up

0 6 12 18 24 48

Study Weeks

4.5 MIU IFN α-2a tiw

90 µg PEGASYS qw

180 µg PEGASYS qw

270 µg PEGASYS qw

Cooksley J Viral Hepat. 2003
End-of-Follow-up
Combined Response*

**Patients with response(%)**

- **4.5 MIU IFN α-2a**: 12%
- **90 µg**: 27%
- **180 µg**: 28%
- **270 µg**: 19%

*HBeAg loss, HBV DNA < 500,000 cps/mL, ALT normalization*
PEGASYS in CHB: Phase III Study Designs

HBeAg-negative CHB – ITT population: n=537
HBeAg-positive CHB – ITT population: n=814

PEGASYS 180 μg qw + oral placebo qd
PEGASYS 180 μg qw + lamivudine 100 mg qd
Lamivudine 100 mg qd

Randomised
End of Treatment 48 weeks
End of Follow-up 72 weeks

Marcellin et al. NEJM 2004; Lau et al. NEJM 2005
Endpoints of PEGASYS Studies
(24 Weeks Post-treatment)

HBeAg-negative CHB – primary endpoints
  • Normal ALT
  • HBV DNA <20,000 cp/mL

HBeAg-positive CHB – primary endpoints
  • HBeAg-seroconversion
  • HBV DNA <100,000 cp/mL
Asian Populations in PEGASYS Studies

- **Asian patients**: 61% (332/537) for HBeAg-negative CHB, 87% (708/814) for HBeAg-positive CHB
- **Non-Asian patients**: 39% (322/814) for HBeAg-negative CHB, 13% (66/814) for HBeAg-positive CHB
HBV DNA Levels Over Time plus HBeAg Seroconversion at End of Follow-up

*all numbers shown are log_{10} reduction from baseline

Mean HBV DNA (log_{10} copies/mL)

On-treatment

Follow-up

HBeAg Seroconversion Rates at End of Follow-up

PEGASYS n=271

PEGASYS + LAM n=271

LAM n=272

32%

27%

19%

P<0.001

P=0.023
End of Treatment HBeAg seroconversion in Relation to Extent of HBV DNA Suppression

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No DNA &lt;400cp/ml</th>
<th>HBeAg seroconversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV</td>
<td>354</td>
<td>21</td>
</tr>
<tr>
<td>LAM</td>
<td>355</td>
<td>18</td>
</tr>
<tr>
<td>LAM</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Peg-2a + LAM</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Peg-2a</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Peg-2b</td>
<td>136</td>
<td>22</td>
</tr>
<tr>
<td>Peg-2b + LAM</td>
<td>130</td>
<td>25</td>
</tr>
</tbody>
</table>


Treatments: ETV, LAM, Peg-2a, Peg-2b, Peg-2b + LAM

Data sources:
- Chang (NEJM 2006)
- Lau (NEJM 2005)
- Janssen (Lancet 2005)
# Sustained HBsAg Loss and Seroconversion (24 Weeks Post-treatment)

<table>
<thead>
<tr>
<th></th>
<th>PEGASYS + placebo (n=271)</th>
<th>PEGASYS + lamivudine (n=271)</th>
<th>Lamivudine (n=272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg loss, n (%)</td>
<td>9 (3%)</td>
<td>11 (4%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P=0.012$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P=0.033$</td>
<td></td>
</tr>
<tr>
<td>HBsAg seroconversion, n (%)</td>
<td>8 (3%)</td>
<td>8 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P=0.004$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P=0.004$</td>
<td></td>
</tr>
</tbody>
</table>

Lau et al. *NEJM* 2005
HBV DNA Suppression in Patients Achieving HBeAg Seroconversion

On-treatment Follow-up

Mean HBV DNA (log₁₀ copies/mL)

0 6 12 18 24 30 36 42 48 54 60 66 72

0 2 4 6 8 10 12

patients with HBeAg seroconversion maintained DNA levels <10,000 cp/mL

Fried et al. EASL 2005
Incidence of Hepatocellular Carcinoma (HCC) by HBV DNA Level

Cumulative Incidence of HCC (%)*

<table>
<thead>
<tr>
<th>Level of HBV DNA (cp/mL)</th>
<th>Cumulative Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR negative</td>
<td>1.30</td>
</tr>
<tr>
<td>&lt;10⁴</td>
<td>1.37</td>
</tr>
<tr>
<td>10⁴–10⁵</td>
<td>3.57</td>
</tr>
<tr>
<td>10⁵–10⁶</td>
<td>12.17</td>
</tr>
<tr>
<td>≥10⁶</td>
<td>14.89</td>
</tr>
</tbody>
</table>

*at the end of the 19th year of follow-up

Chen et al. JAMA 2006
Efficacy of PEGASYS in HBeAg-negative CHB
Combined Response* 24 Weeks Post-treatment: HBeAg-negative CHB

- **PEGASYS + placebo**: 36% (n=177)
- **PEGASYS + lamivudine**: 38% (n=179)
- **Lamivudine**: 23% (n=181)

*ALT normalisation and HBV DNA <20,000 cp/mL

Marcellin et al. *NEJM* 2004
### Sustained HBsAg Seroconversion: HBeAg-negative CHB

24 Weeks Post-treatment (Week 72)

<table>
<thead>
<tr>
<th></th>
<th>PEGASYS + placebo</th>
<th>PEGASYS + lamivudine</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg seroconversion, n (%)</td>
<td>5/177 (3%)</td>
<td>3/179 (2%)</td>
<td>0/181 (0%)</td>
</tr>
</tbody>
</table>

* Fisher’s Exact Test

P = 0.029

Marcellin et al. *NEJM* 2004
Predictors of Response
### Significant* Baseline Predictors of Response
**24 Weeks Post-treatment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HBeAg-negative (combined response**)</th>
<th>HBeAg-positive (HBeAg seroconversion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEGASYS treatment (vs. lam)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Age (young &gt; old)</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Gender (female &gt; male)</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Bodyweight</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Baseline ALT (high &gt; low)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Baseline HBV DNA (low &gt; high)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Baseline HBeAg (low &gt; high)</td>
<td>na</td>
<td>✓</td>
</tr>
<tr>
<td>Genotype</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

*P<0.05 by MV analysis; **ALT normalisation and HBV DNA <20,000 cp/mL

Roche data on file
Safety of PEGASYS in CHB
## Common Adverse Events* with PEGASYS Monotherapy in CHB

<table>
<thead>
<tr>
<th></th>
<th>HBeAg-negative(^1)</th>
<th>HBeAg-positive(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=177</td>
<td>n=271</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>59%</td>
<td>49%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>42%</td>
<td>40%</td>
</tr>
<tr>
<td>Headache</td>
<td>24%</td>
<td>28%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>27%</td>
<td>26%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18%</td>
<td>15%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>14%</td>
<td>20%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11%</td>
<td>9%</td>
</tr>
</tbody>
</table>

*Considered by the investigator to be related to therapy (≥10% incidence)

# Deaths

<table>
<thead>
<tr>
<th></th>
<th>PEGASYS + placebo</th>
<th>PEGASYS + lamivudine</th>
<th>lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg-negative CHB¹</td>
<td>n=177</td>
<td>n=179</td>
<td>n=181</td>
</tr>
<tr>
<td></td>
<td>1*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>n=271</td>
<td>n=271</td>
<td>n=272</td>
</tr>
<tr>
<td>HBeAg-positive CHB²</td>
<td>0</td>
<td>3**</td>
<td>1***</td>
</tr>
</tbody>
</table>

* thrombotic thrombocytopenic purpura
** three deaths in combination group were unrelated to therapy (two car accidents and one house fire [septic shock])
** two patients in lamivudine group had liver failure after cessation of therapy – one liver transplant and one death

Durability
Long-term Follow-up Study: 1-year Analysis


** 1-year analysis of patients from initial study who completed 6-month follow-up
HBeAg Seroconversion: 40% of Asian Patients Achieved Sustained Responses 1 year Post-treatment

- Over 80% of patients with responses 6 months post-treatment sustained these responses 1 year post-treatment.

Initial study
- Week 48: 31% (n=238)

Entered long-term study
- Week 72: 39% (n=58/150)
- Week 96: 40% (n=60/150, 83% sustained)

Lau et al. Shanghai Hong Kong Liver Congress 2006
HBV DNA Levels 1 Year Post-treatment According to Type of Response

According to Type of Response

- **Sustained HBeAg Seroconversion** (n=53)
  - <=400: 38
  - 401 to 10'000: 23
  - 10'001 to 100'000: 10
  - >100'000: 21

- **Late HBeAg Seroconversion** (n=13)
  - <=400: 23
  - 401 to 10'000: 31
  - 10'001 to 100'000: 10
  - >100'000: 23

- **No HBeAg Seroconversion** (n=67)
  - <=400: 99
  - 401 to 10'000: 0
  - 10'001 to 100'000: 0
  - >100'000: 0
ALT (median) Over Time in Asian Patients Participating in Long Terms Study According to Type of Response

- HBeAg seroconversion at week 72 or before and sustained over FU period (n=53)
- Late HBeAg seroconversion (after week 72; n=14)
- No HBeAg seroconversion (n=78)
HBV DNA Profiles During the 1 Year Follow-up Period: PEGASYS Monotherapy

Response Patterns A & B and Relapsers

- Patients with relapse (n=40)
- Patients with response pattern A (n=22)
  - (HBV DNA peaks 20,000–100,000 cp/mL)
- Patients with response pattern B (n=27)
  - (HBV DNA peaks <20,000 cp/mL)

Mean HBV DNA (log_{10} copies/mL)

0 1 2 3 4 5 6 7

0 1 2 3 4 5 6 7

Months after EOT

0 1 2 3 4 5 6 7

100,000 cp/mL

400 cp/mL
Treatment Algorithm to Improve Clinical Outcomes

1st choice
Aiming for sustained remission
Using a treatment of finite duration
eg pegylated or conventional IFNα

Sustained remission → yes

no*

Survival

2nd choice
Maintained remission
Using a treatment of indefinite duration
eg nucleos(t)ide analogues

*or IFNα contraindicated / not tolerated
Innate Immunity

• Recently TLRs, especially TLR3, TLR7 and TLR9, found to be key receptors for viral infections
• Previously, role in HBV uncertain

Medzhitov et al., Nature Immunology 2001
Toll-like receptor-7, CD4+ and CD8+ T cell reactivity in HBsAg Seroconverters with Pegasys®

Increased TLR7 in HBsAg clearers

Increased HBV specific CD4+ T cells in HBsAg clearance

Increased HBV specific CD8+ T cells in HBsAg clearance

Hui et al., AASLD 2005#1291
Treatment of CHB-2006 and beyond

No established treatment
Trials with IFN-α

1980

1990

IFN-α

LAM

ADV

ETV

pIFN-α2a

Combination therapy

2000

2010

Immunomulators
Non-specific immunotherapy
• Interleukin-12/ interleukin-18
• Thymosin-alfa
• TLR-agonist

HBV-specific immunotherapy
• HBs antibodies
• HBV protein vaccine (Surface; Core)
• HBV DNA vaccine
• T-cell expansion ex vivo
• Dendritic cell immunotherapy

Antivirals
Direct anti-viral
• Pradefovir, Tenofovir, L-FMAU
• L-dT, L-dC, L-dA

Viral packaging inhibitors
• AT-61; AT 130 (RNA encapsidation)
• Bay 41- 4109 (Core degradation)

Gene therapy
• siRNA
• antisense oligonucleotides