Peginterferon alfa-2a (Pegasys)

Prepared by: David Spach, MD & H. Nina Kim, MD
Last Updated: February 14, 2014
Peginterferon alfa-2a versus Interferon alfa-2a
Study Features

- **Study**
  - Randomized, open label, parallel dose, phase 3 trial
  - 36 international centers

- **Subjects**
  - N = 531 with chronic hepatitis C
  - Treatment naïve
  - Any genotype (62% with genotype 1)
  - 18 years of age or older

- **Regimens**
  - Peginterferon alfa-2a: 180 μg 1x/week x 48 weeks
  - Interferon alfa-2a: 6 million units 3x/week x 12 weeks, then 6 million units 3x/week x 36 weeks

- **Primary Endpoint: Sustained Virologic Response (SVR24)**
  - SVR = undetectable serum HCV RNA 24 weeks after 48-week treatment
  - Undetectable serum HCV RNA = less than 100 copies/ml

Peginterferon alfa-2a versus Interferon alfa-2a Study Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>24</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>267</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peginterferon alfa-2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>264</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon alfa-2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug Dosing
- Peginterferon alfa-2a: 180 µg once weekly
- Interferon alfa-2a: 6 million units 3x/week x 12 weeks, then 6 million units 3x/week x 36 weeks

Peginterferon alfa-2a versus Interferon alfa-2a Study Results

Virologic Responses by Treatment Regimen (ITT Analysis)

Peginterferon alfa-2a versus Interferon alfa-2a Study Results

Independent Factors Associated with SVR, Multiple Regression Analysis

- Age ≤ 40 years
- No cirrhosis or bridging fibrosis
- Body-surface area ≤ 2 m²
- Treatment with peginterferon alfa-2a
- HCV RNA level ≤ 2 million copies/ml
- Pretreatment ALT quotient > 3
- HCV genotype other than type 1

Conclusions: “In patients with chronic hepatitis C, a regimen of peginterferon alfa-2a given once weekly is more effective than a regimen of interferon alfa-2a given three times weekly.”

Treatment Naïve, Chronic HCV

Peginterferon alfa -2a+/- Ribavirin

versus

Interferon alfa-2b + Ribavirin

Peginterferon +/- Ribavirin versus Interferon + Ribavirin
Study Features

• **Study**
  - Open-label randomized controlled trial

• **Subjects**
  - N = 1149 with chronic hepatitis C randomized
  - Treatment naïve; 62% genotype 1
  - Serum ALT above upper limit of normal x prior 6 months

• **Regimens (48 Week Treatment)**
  - Peginterferon alfa-2a 180 μg 1x/week + Ribavirin 1000-1200 mg/day
  - Peginterferon alfa-2a 180 μg 1x/week + Placebo
  - Interferon alfa-2b 3 million U 3x/week + Ribavirin 1000-1200 mg/day

• **Primary Endpoint**
  - Undetectable serum HCV RNA 24 weeks after stopping treatment

*Ribavirin dosing: <75 kg: 1000 mg/day; ≥75 kg: 1200 mg/day

Peginterferon +/- Ribavirin versus Interferon + Ribavirin Study Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>453</td>
<td>Peginterferon alfa-2a + Ribavirin</td>
<td>SVR24</td>
</tr>
<tr>
<td>N</td>
<td>224</td>
<td>Peginterferon alfa-2a + Placebo</td>
<td>SVR24</td>
</tr>
<tr>
<td>N</td>
<td>444</td>
<td>Interferon alfa-2b + Ribavirin</td>
<td>SVR24</td>
</tr>
</tbody>
</table>

Drug Dosing
Peginterferon alfa-2a 180 µg 1x/week
Weight-based Ribavirin (divided bid): 1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg
Interferon alfa-2b 3 million U 3x/week

Peginterferon +/- Ribavirin versus Interferon + Ribavirin Results

Virologic Responses, by Treatment Regimen

Conclusions: “In patients with chronic hepatitis C, once-weekly peginterferon alfa-2a plus ribavirin was tolerated as well as interferon alfa-2b plus ribavirin and produced significant improvements in the rate of sustained virologic response, as compared with interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone.”

Peginterferon alfa-2a (Pegasys)

Background and Dosing
Treatment Naïve, Chronic HCV

Duration and Dose Finding Peginterferon alfa-2a + Ribavirin
Randomized study of low-dose versus weight based ribavirin and 24 versus 48 weeks of therapy

Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose

- **Study**
  - Randomized, double-blind trial, with 2 x 2 factorial design

- **Subjects**
  - N = 1311 with chronic hepatitis C (1284 treated)
  - Treatment naïve adult patients; 58% genotype 1
  - Serum ALT above upper limit of normal x prior 6 months

- **Regimens**
  - Peginterferon alfa-2a: 180 μg/wk + Ribavirin: 800 mg/day x 24 wks
  - Peginterferon alfa-2a: 180 μg/wk + *Ribavirin: 1000-1200 mg/day x 24 wks
  - Peginterferon alfa-2a: 180 μg/wk + Ribavirin: 800 mg/d x 48 weeks
  - Peginterferon alfa-2a: 180 μg/wk + *Ribavirin: 1000-1200 mg/day x 48 wks

- **Primary Endpoint**
  - Undetectable serum HCV RNA at end of treatment (ETR)
  - Undetectable serum HCV RNA 24 wks after cessation of treatment (SVR)

*Ribavirin dose: Ribavirin 1000 mg/day for Wt <75 kg, 1200 mg/day for Wt ≥75 kg

Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose

Week 0
Randomize

Peginterferon alfa-2a + Ribavirin (low dose) (n = 214)
SVR24

Peginterferon alfa-2a + Ribavirin (weight-based dose) (n = 288)
SVR24

Peginterferon alfa-2a + Ribavirin (low dose) (n = 365)
SVR24

Peginterferon alfa-2a + Ribavirin (weight-based dose) (n = 444)
SVR24

Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose

SVR24 Rates, by Regimen

Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose

Rates of SVR with Different Peginterferon + Ribavirin Regimens

- Peginterferon + Ribavirin (low dose) x 24 weeks
- Peginterferon + Ribavirin (weight-based dose) x 24 weeks
- Peginterferon + Ribavirin (low dose) x 48 weeks
- Peginterferon + Ribavirin (weight-based dose) x 48 weeks

<table>
<thead>
<tr>
<th>Patients with SVR (%)</th>
<th>Low Viral Load...</th>
<th>High Viral Load...</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>84 81 79 80</td>
<td>84 80 74 82</td>
</tr>
<tr>
<td>Low Viral Load...</td>
<td>85 83 88 77</td>
<td></td>
</tr>
<tr>
<td>(≤ 2 x 10^6 copies/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Viral Load...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt; 2 x 10^6 copies/ml)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: “Treatment with peginterferon-alpha2a and ribavirin may be individualized by genotype. Patients with HCV genotype 1 require treatment for 48 weeks and a standard dose of ribavirin; those with HCV genotypes 2 or 3 seem to be adequately treated with a low dose of ribavirin for 24 weeks.”

Peginterferon alfa-2b + RBV vs. Peginterferon alfa-2a + RBV
IDEAL STUDY

Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin

IDEAL Study: Design

- **Study**
  - Randomized comparative trial
  - 118 centers in United States

- **Subjects**
  - N = 3070 with chronic hepatitis C
  - All genotype 1 (other genotypes excluded)
  - Treatment naïve
  - Subjects were 18 years of age or older

- **Regimens (Ribavirin Dosed by Weight)**
  - Peginterferon alfa-2b: 1.5 μg/kg 1x/week + Ribavirin 800-1400 mg/day*
  - Peginterferon alfa-2b: 1.0 μg/kg 1x/week + Ribavirin 800-1400 mg/day*
  - Peginterferon alfa-2a: 180 μg 1x/week + Ribavirin 1000-1200 mg/day^*

- **Primary Endpoint (Sustained Virologic Response [SVR])**
  - SVR = Undetectable serum HCV RNA 24 weeks after 48-week treatments

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*Ribavirin dosing: 40-65 kg: 800 mg/d; >65-85 kg: 1000 mg/d; >85-105 kg: 1200 mg/d; >105-120 kg: 1400 mg/d

^Ribavirin dosing: < 75 kg: 1000 mg/d; ≥ 75 kg: 1200 mg/d

Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin

IDEAL Study: Design

Week 0

N = 1019
Standard-Dose Peginterferon alfa-2b + Ribavirin
Peginterferon alfa-2b: 1.5 μg/kg 1x/week + Ribavirin: 800-1400 mg/d (by weight)
SVR24

N = 1016
Low-Dose Peginterferon alfa-2b + Ribavirin
Peginterferon alfa-2b: 1.0 μg/kg 1x/week + Ribavirin: 800-1400 mg/d (by weight)
SVR24

N = 1035
Peginterferon alfa-2a + Ribavirin
Peginterferon alfa-2a: 180 μg 1x/week + Ribavirin: 1000-1200 mg/d (by weight)
SVR24

Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin

IDEAL Study: Results

IDEAL Study: Virologic Responses by Treatment Regimen

Peginterferon alfa-2a (Pegasys) Summary

• Approval Status: FDA approved in 2002

• Indications:
  - In combination with ribavirin for all genotypes
  - In combination with ribavirin plus protease inhibitor for GT1

• Class & Mechanism
  - Complex mechanism based on altering immune response to HCV infection

• Dosing:
  - 180 mcg subcutaneously once per week
  - Duration dependent on genotype and remaining components of regimen

• Adverse Effects (AE)
  - Extensive adverse effects
  - Influenza-like symptoms
  - Depression
  - Hematologic (leukopenia and thrombocytopenia)
  - Thyroid dysfunction

Source: Peginterferon alfa-2a (Pegasys) Prescribing Information. Genentech USA.
Peginterferon alfa-2b + Ribavirin vs Interferon alfa-2a + Ribavirin

IDEAL Study: Results

IDEAL Study: Serious Adverse Event Rates

- Standard-dose Peginterferon alfa-2b + Ribavirin
- Low-dose Peginterferon alfa-2b + Ribavirin
- Peginterferon alfa-2a + Ribavirin

Treatment-Related Serious Adverse Event:
- Standard-dose: 3.9%
- Low-dose: 4.4%
- Peginterferon alfa-2a: 4.4%

Hematologic Serious Adverse Event:
- Standard-dose: 0.4%
- Low-dose: 0.4%
- Peginterferon alfa-2a: 0.8%

Conclusions: “In patients infected with HCV genotype 1, the rates of sustained virologic response and tolerability did not differ significantly between the two available peginterferon-ribavirin regimens or between the two doses of peginterferon alfa-2b.”

Treatment Naïve, Chronic HCV and HIV

PEG alfa-2a + RBV versus PEG alfa-2a versus INF + RBV
APRICOT STUDY

PEG + RBV versus PEG versus INF + RBV in HCV & HIV
APRICOT Study: Features

• Study
  - Randomized, placebo-controlled trial
  - Conducted at 95 centers in 19 countries in U.S., Canada, & Europe

• Subjects
  - N = 868 chronically infected with both HCV and HIV
  - Treatment naïve; 61% genotype 1
  - CD4 >200 cells/mm³ or
    CD4 = 100-200 cells/mm³ + HIV RNA level <5,000 copies/ml

• Regimens (48 Week Treatment)
  - Peginterferon alfa-2a 180 μg 1x/week + Ribavirin 800 mg/day
  - Peginterferon alfa-2a 180 μg 1x/week + Placebo
  - Interferon alfa-2a: 3 million IU 3x/week + Ribavirin 800 mg/day

• Primary Endpoint
  - Undetectable HCV RNA (< 50 IU/ml) 24 weeks after stopping Rx
PEG + RBV versus PEG versus INF + RBV in HCV & HIV
APRICOT Study: Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 289</td>
<td>Peginterferon alfa-2a + Ribavirin</td>
<td>SVR24</td>
<td></td>
</tr>
<tr>
<td>N = 286</td>
<td>Peginterferon alfa-2a + Placebo</td>
<td>SVR24</td>
<td></td>
</tr>
<tr>
<td>N = 285</td>
<td>Interferon alfa-2a + Ribavirin</td>
<td>SVR24</td>
<td></td>
</tr>
</tbody>
</table>

Drug Dosing
Peginterferon alfa-2a 180 μg 1x/week
Ribavirin (divided bid): 800 mg/day
Interferon alfa-2a 3 million IU 3x/week

PEG + RBV versus PEG versus INF + RBV in HCV & HIV
APRICOT Study: Results

APRICOT Study: Virologic Responses by Treatment Regimen

End of Treatment Response

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon + Ribavirin</td>
<td>47</td>
<td>136/289</td>
</tr>
<tr>
<td>Peginterferon + Placebo</td>
<td>31</td>
<td>90/286</td>
</tr>
<tr>
<td>Interferon + Ribavirin</td>
<td>14</td>
<td>40/285</td>
</tr>
</tbody>
</table>

Sustained Virologic Response-24

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon + Ribavirin</td>
<td>40</td>
<td>116/289</td>
</tr>
<tr>
<td>Peginterferon + Placebo</td>
<td>20</td>
<td>58/286</td>
</tr>
<tr>
<td>Interferon + Ribavirin</td>
<td>12</td>
<td>33/285</td>
</tr>
</tbody>
</table>

PEG + RBV versus PEG versus INF + RBV in HCV & HIV

APRICOT Study: Results

APRICOT Study: SVR24 by Treatment Regimen and Genotype

PEG + RBV versus PEG versus INF + RBV in HCV & HIV
APRICOT: Predictive Value of Early Virologic Response

**Peginterferon alfa-2a + Ribavirin**

- **Week 12**
  - HCV RNA (N = 289)

- **2-log drop or undetectable HCV RNA**
  - Yes
    - N = 204 (71%)
      - SVR: N = 114 (56%)
      - No SVR: N = 90 (44%)
  - No
    - N = 85 (29%)
      - SVR: N = 2 (2%)
      - No SVR: N = 83 (98%)

**Conclusions:** “Among patients infected with both HIV and HCV, the combination of peginterferon alfa-2a plus ribavirin was significantly more effective than either interferon alfa-2a plus ribavirin or peginterferon alfa-2a monotherapy.”

Treatment Naïve, Chronic HCV and HIV

Peginterferon alfa-2a + RBV versus Interferon alfa-2a + RBV
ACTG 5071

Interferon alfa engages receptors on the surface of the hepatocyte, initiating intracellular signal transduction that prompts the transcription of multiple interferon-stimulated genes (ISGs). These ISGs encode proteins that can interfere at various stages of the hepatitis C viral life cycle.

PEG alfa-2a + RBV versus IFN alfa-2a + RBV in HCV & HIV

ACTG 5071 Study: Features

- **Study**
  - Randomized, placebo-controlled, phase 2 trial
  - Conducted at 21 ATG sites in United States

- **Subjects**
  - N = 133 chronically infected with both HCV and HIV
  - Treatment naïve
  - 78% genotype 1

- **Regimens (48 Week Treatment)**
  - Peginterferon alfa-2a 180 μg 1x/week + Ribavirin (dose escalation)
  - Interferon alfa-2a: 6 million IU 3x/week, then 3 million IU 3x/week + Ribavirin (dose escalation)

- **Primary Endpoint**
  - Undetectable HCV RNA (< 50 IU/ml) 24 weeks after stopping Rx

PEG alfa-2a + RBV versus IFN alfa-2a + RBV in HCV & HIV
ACTG 5071 Study: Design

Drug Dosing
Peginterferon alfa-2a 180 µg 1x/week x 48 weeks
Interferon alfa-2a 6 million IU 3x/week x 12 weeks, then 6 million IU 3x/week x 36 weeks
Ribavirin (divided bid): 600 mg/day x 4 weeks, then 800 mg/day x 4 weeks, then 1000 mg/day x 40 weeks

PEG alfa-2a + RBV versus IFN alfa-2a + RBV in HCV & HIV
ACTG 5071 Study: Results

ACTG 5071 Study: Virologic Responses by Treatment Regimen

PEG alfa-2a + RBV versus IFN alfa-2a + RBV in HCV & HIV
ACTG 5071 Study: Results

ACTG 5071 Study: SVR24 by Treatment Regimen and Genotype

PEG alfa-2a + RBV versus IFN alfa-2a + RBV in HCV & HIV
ACTG 5071: Predictive Value of Early Virologic Response

Week 12
HCV RNA (N = 106)

2-log drop or undetectable HCV RNA

Yes
N = 43 (42%)
SVR
N = 22 (51%)
No SVR
N = 21 (49%)

No
N = 63 (59%)
SVR
N = 0 (0%)
No SVR
N = 63 (100%)

Conclusions: “In persons infected with HIV, the combination of peginterferon and ribavirin is superior to the combination of interferon and ribavirin in the treatment of chronic hepatitis C. These regimens may provide clinical benefit even in the absence of virologic clearance. The marked discrepancy in the rates of sustained virologic response between HCV genotypes indicates that strategies are needed to improve the outcome in persons infected with HCV genotype 1.”

This slide deck is from the University of Washington’s *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online
www.hepatitisc.uw.edu

Hepatitis Web Study
http://depts.washington.edu/hepstudy/

Funded by a grant from the Centers for Disease Control and Prevention.
Peginterferon alfa-2a (Pegasys) Contraindications

- Autoimmune hepatitis
- Hepatic decompensation in patients with cirrhosis
- Use in neonates/infants
- Known hypersensitivity reaction
- Additional contraindications when used with ribavirin
  - Pregnant women and men whose female partners are pregnant
  - Hemoglobinopathies
  - Co-administration with didanosine

Source: Peginterferon alfa-2a (Pegasys) Prescribing Information. Genentech USA.
## Peginterferon alfa-2a Hematologic Dose Modification Guidelines for Adults

<table>
<thead>
<tr>
<th>Laboratory Value</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &lt;750 cells/mm³</td>
<td>Reduce to 135 mcg</td>
</tr>
<tr>
<td>ANC &lt;500 cells/mm³</td>
<td>Discontinue treatment until ANC values return to more than 1000 cells/mm³. Reintroduce at 90 mcg and monitor ANC.</td>
</tr>
<tr>
<td>Platelet &lt;50,000 cells/mm³</td>
<td>Reduce to 90 mcg</td>
</tr>
<tr>
<td>Platelet &lt;25,000 cells/mm³</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>

**Source:** Peginterferon alfa-2a (Pegasys) Prescribing Information. Genentech.
### Peginterferon alfa-2a Dose Modification Guidelines for Adults with Depression

<table>
<thead>
<tr>
<th>Depression Severity</th>
<th>Initial Management (4-8 weeks)</th>
<th>Depression Status</th>
<th>Worsens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose Modification</td>
<td>Remains Stable</td>
<td>Improves</td>
</tr>
<tr>
<td>Mild</td>
<td>No change</td>
<td>Continue weekly visit schedule</td>
<td>Resume normal visit schedule</td>
</tr>
<tr>
<td>Moderate</td>
<td>Decrease peginterferon alfa-2a dose to 135 mcg (in some cases dose reduction to 90 mcg may be needed)</td>
<td>Evaluate once weekly by visit and/or phone</td>
<td>Consider psychiatric Consultation. Continue reduced dosing</td>
</tr>
<tr>
<td>Severe</td>
<td>Discontinue peginterferon alfa-2a permanently</td>
<td>Obtain immediate psychiatric consultation</td>
<td>Psychiatric therapy necessary</td>
</tr>
</tbody>
</table>

Source: Peginterferon alfa-2a (*Pegasys*) Prescribing Information. Genentech.
Peginterferon alfa-2a Hematologic Dose Modification Guidelines for Adults with Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Peginterferon alfa-2a Dose (once weekly)</th>
<th>Ribavirin* (Copegus) Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-50 mL/min</td>
<td>180 mcg</td>
<td>Alternating doses, 200 mg and 400 mg every other day</td>
</tr>
<tr>
<td>&lt; 30 mL/min</td>
<td>135 mcg</td>
<td>200 mg daily</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>135 mcg</td>
<td>200 mg daily</td>
</tr>
</tbody>
</table>

*Note: Other preparations of ribavirin (Rebetol, Ribasphere) are contraindicated for use with Creatinine clearance < 50 mL/min

Source: Peginterferon alfa-2a (Pegasys) Prescribing Information. Genentech.
Peginterferon alfa-2a

versus

Interferon alfa-2a