Ribavirin (*Copegus, Rebetol, Ribasphere*)

Prepared by: David Spach, MD and H. Nina Kim, MD
Last Updated: February 14, 2014
Conclusions: “In patients with chronic hepatitis C, initial therapy with interferon and ribavirin was more effective than treatment with interferon alone.”
Phase 3

Treatment Naïve, Chronic HCV

Peginterferon alfa-2a +/- Ribavirin for Chronic HCV

Peginterferon alfa-2a +/- Ribavirin for Chronic HCV Study Design

- **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 alfa-2a +/- Ribavirin for Chronic HCV Study Design

<table>
<thead>
<tr>
<th>Week</th>
<th>N</th>
<th>Arm</th>
<th>SVR24</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>453</td>
<td>Peginterferon alfa-2a + Ribavirin</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>224</td>
<td>Peginterferon alfa-2a + Placebo</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>444</td>
<td>Standard interferon + Ribavirin</td>
<td></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 alfa-2a + Ribavirin for Chronic HCV

Results

Response after 48 Weeks of Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
<th>(\text{End of Treatment Response})</th>
<th>(\text{Sustained Virologic Response})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a 180 µg + Ribavirin</td>
<td>59%</td>
<td>313/453</td>
<td>56%</td>
</tr>
<tr>
<td>Peginterferon alfa-2a 180 µg + Placebo</td>
<td>52%</td>
<td>132/224</td>
<td>29%</td>
</tr>
<tr>
<td>Interferon alfa-2b + Ribavirin</td>
<td>44%</td>
<td>231/444</td>
<td>44%</td>
</tr>
</tbody>
</table>

**Peginterferon alfa-2a + Ribavirin for Chronic HCV**

**Predictive Value of Early Virologic Response**

- **Week 12**
  - HCV RNA (N = 453)

- **2-log drop or undetectable HCV RNA**
  - Yes
    - N = 390 (86%)
      - SVR
        - N = 253 (65%)
        - No SVR
          - N = 137 (35%)
  - No
    - N = 63 (14%)
      - SVR
        - N = 2 (3%)
      - No SVR
        - N = 61 (97%)

**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.”

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

- **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 (SV

*Ribavirin dose: 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 12 24 48 72
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 = 158) → SVR24

Ribavirin (Copegus, Rebetol, Ribasphere)

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

SVR24 Rates, by Regimen

- PEG + RBV (low dose) x 24 weeks
- PEG + RBV (weight-based dose) x 24 weeks
- PEG + RBV (low dose) x 48 weeks
- PEG + RBV (weight-based dose) x 48 weeks

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

Patients with SVR (%)

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Low Viral Load</th>
<th>High Viral Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon + Ribavirin (low dose) x 24 weeks</td>
<td>84</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>Peginterferon + Ribavirin (weight-based dose) x 24 weeks</td>
<td>81</td>
<td>83</td>
<td>80</td>
</tr>
<tr>
<td>Peginterferon + Ribavirin (low dose) x 48 weeks</td>
<td>79</td>
<td>88</td>
<td>77</td>
</tr>
<tr>
<td>Peginterferon + Ribavirin (weight-based dose) x 48 weeks</td>
<td>80</td>
<td>88</td>
<td>82</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.”

Treatment Naïve, Chronic HCV

WINR Study
Flat versus Weight-Based Ribavirin Dosing

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Design

- **Study**
  - Prospective, randomized, open-label trial

- **Subjects**
  - N = 5027 with chronic hepatitis C (4913 analyzed)
  - Treatment naïve adult patients (Age 18-70)

- **Treatment Regimens**
  - Peginterferon alfa-2b: 1.5 μg/kg/wk + Wt-based* Ribavirin: 800-1400 mg/d
  - Peginterferon alfa-2b: 1.5 μg/kg/wk + Flat-dose Ribavirin: 800 mg/d

- **Treatment Duration**
  - Genotypes 1,4,5,6: duration of 48 weeks
  - Genotypes 2,3: duration of 24 or 48 weeks

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

*Weight-based ribavirin dosing: < 65 kg: 800 mg/d; 65-85 kg: 1000 mg/d; >85-105 kg: 1200 mg/d; >105 kg: 1400 mg/d

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose)

WIN-R 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>GT 1-6</td>
<td></td>
<td></td>
<td></td>
<td>SVR24</td>
</tr>
<tr>
<td>PEG + Ribavirin (weight-based)</td>
<td>(n = 2111)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT 2, 3</td>
<td></td>
<td></td>
<td></td>
<td>SVR24</td>
</tr>
<tr>
<td>PEG + RBV (weight-based)</td>
<td>(n = 333)</td>
<td></td>
<td></td>
<td>SVR24</td>
</tr>
<tr>
<td>PEG + Ribavirin (flat dose)</td>
<td>(n = 335)</td>
<td></td>
<td></td>
<td>SVR24</td>
</tr>
<tr>
<td>SVR24</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Drug Dosing

Peginterferon alfa-2b: 180 μg once weekly
Weight-based Ribavirin (in 2 divided doses):
- 800 mg/d if < 65 kg; 1000 mg/d if 65-85 kg; 1200 mg/d if >85-105 kg; 1400 mg/d if >105 kg
Flat-dose Ribavirin (in 2 divided doses): 800 mg/day

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Results

SVR 24, by Genotype and Treatment Regimen

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Results

All Treated: SVR24 by Weight Distribution

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Results

Genotype 1: SVR24 by Weight Distribution

Peginterferon alfa-2b & Weight-based or Flat-dose Ribavirin
WIN-R Study: Results

Genotypes 2,3: SVR24 by Weight Distribution

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose)
WIN-R Study: Results

Sustained Virologic Response (SVR) by Weight Distribution

**African American Genotype 1**

**Weight-Based Ribavirin**
- 65-85 kg: 13.1%
- >85-105 kg: 22.2%
- >105 kg: 31.3%

**Flat-Dose Ribavirin**
- 65-85 kg: 11.7%
- >85-105 kg: 9.9%
- >105 kg: 6.7%

**P = .036**
**P = .446**

Peginterferon alfa-2b & Weight-based or Flat-dose Ribavirin
WIN-R Study: Results

Relapse Rates among Patients who Achieved End-of-Treatment Responses

Conclusion: “Peginterferon alfa-2b plus weight-based ribavirin is more effective than flat-dose ribavirin, particularly in genotype 1 patients, providing equivalent efficacy across all weight groups. Ribavirin 1400 mg/day is appropriate for patients 105 to 125 kg. For genotype 2/3 patients, 24 weeks of treatment with flat-dose ribavirin is adequate; no evidence of additional benefit of extending treatment to 48 weeks was demonstrated.”

This slide deck is from the University of Washington’s \textit{Hepatitis C Online} and \textit{Hepatitis Web Study} projects.

\textbf{Hepatitis C Online}  
\url{www.hepatitisc.uw.edu}

\textbf{Hepatitis Web Study}  
\url{http://depts.washington.edu/hepstudy/}

Funded by a grant from the Centers for Disease Control and Prevention.
Ribavirin (*Copegus, Rebetol, Ribasphere*)

- **Mechanism**: purine nucleoside analog

- **Approval Status**:
  - First approved by FDA in 1998
  - Multiple preparations subsequently FDA approved

- **Indications**
  - In combination with other agents for all HCV genotypes

- **Dosing** (brand dependent):
  - Fixed dose (800 mg PO per day in two divided doses)
  - Weight based (1000-1200 mg per day in two divided doses)
  - Weight based (800-1400 mg per day in two divided doses)

- **Drug Interactions**
  - Use of ribavirin and didanosine can cause life-threatening toxicity
  - Use of ribavirin and azathioprine can cause azathioprine-related toxicity

- **Adverse Effects (AE)**
  - Hemolytic anemia
  - Birth defects (pregnancy category X)
Ribavirin: Key Studies

- Interferon alfa-2b +/- Ribavirin for 24 or 48 weeks
- Peginterferon alfa-2a +/- Ribavirin for Chronic HCV
- Duration and Dose Finding Peginterferon alfa-2a + Ribavirin
- Flat versus Weight-Based Ribavirin Dosing: WINR Study
Treatment Naïve, Chronic HCV

Interferon alfa-2b +/- Ribavirin for 24 or 48 weeks

Interferon alfa-2b +/- Ribavirin for Chronic HCV Study Outline

• **Study**
  - Randomized, double-blinded, placebo controlled, phase 3 trial
  - Conducted in 44 centers in United States

• **Subjects**
  - N = 912 with chronic hepatitis C
  - Treatment naïve; 72% genotype 1

• **Regimens**
  - Interferon alfa-2b + Placebo x 24 or 48 weeks
  - Interferon alfa-2b + Ribavirin (weight based) x 24 or 48 weeks

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

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

Interferon alfa-2b +/- Ribavirin for Chronic HCV Study Design

Week 0 → 24 → 48 → 72

- Interferon (n = 231) → SVR24
- Interferon (n = 225) → SVR24
- Interferon + Ribavirin (n = 228) → SVR24

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

Interferon alfa-2b +/- Ribavirin for Chronic HCV Study Results

SVR 24, by Treatment Regimen

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Patients with SVR 24 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon (24 weeks)</td>
<td>6/231 (2.6%)</td>
</tr>
<tr>
<td>Interferon (48 weeks)</td>
<td>13/225 (5.8%)</td>
</tr>
<tr>
<td>Interferon + Ribavirin (24 weeks)</td>
<td>70/228 (30.6%)</td>
</tr>
<tr>
<td>Interferon + Ribavirin (48 weeks)</td>
<td>87/228 (38.2%)</td>
</tr>
</tbody>
</table>