Hepatitis C: Non-responders

Nikunj Shah, MD
Associate Professor of medicine
University of Illinois Medical center

Current Standard of Care for Naïve HCV Patients (SVR)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Peg IFN 2a 180 mcg + 1000-1200/RBV</th>
<th>Peg IFN 2b 1.5 mcg + 800/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR (%)</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>[Pegasys® Package Insert]</td>
<td>[Peg-Intron® Package Insert]</td>
</tr>
</tbody>
</table>

Current Standard of Care for Naïve HCV Genotype 1 Patients (SVR)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Peg IFN 2a 180 mcg + 1000-1200/RBV</th>
<th>Peg IFN 2b 1.5 mcg + 800/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR (%)</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>[Pegasys® Package Insert]</td>
<td>[ Peg-Intron® Package Insert]</td>
</tr>
</tbody>
</table>

HCV Antiviral Therapy: Increasing Rates of Sustained Viral Remission Over the Past 15 Years

PEG IFN-alfa 2b/RBV Weight-Based Dosing

- PEG IFN-alfa 2b/RBV Overall: 61%
- IFN alfa-2b/RBV 48 Wk: 54% - 56%
- IFN alfa-2b/RBV 48 Wk: 41%
- IFN alfa-2b/RBV 48 Wk: 25% - 39%
- IFN alfa-2b/RBV 48 Wk: 15% - 39%

- IFN 24 Wk: 8% - 12%
- IFN 48 Wk: 12% - 22%
- IFN 48 Wk: 25% - 39%
- IFN 48 Wk: 41%
HCV Genotype is the Most Important Predictor of SVR

Factors Predicting a Response to Therapy

**Fixed**
- Genotype
- Level of virus in the blood
  - Usually expressed in millions/IU
- Histology at liver biopsy
- Rapidity of viral clearance

**Variable**
- Type of therapy
  - Dose and duration
- Adherence to therapy
  - Quality of life
- Treating physician

Treatment of IFN α-2 Nonresponders with PEG-IFN α-2a + Ribavirin

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>ETR</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN monotherapy</td>
<td>44%</td>
<td>30%</td>
</tr>
<tr>
<td>IFN + R therapy</td>
<td>30%</td>
<td>11%</td>
</tr>
<tr>
<td>Genotype I</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td>Genotypes 2/3</td>
<td>72%</td>
<td>52%</td>
</tr>
<tr>
<td>Caucasians</td>
<td>37%</td>
<td>20%</td>
</tr>
<tr>
<td>African Americans</td>
<td>14%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Growing Number of Non-responders to Alpha 2 Interferons

What Do We Do Now?
Retreatment Options for Nonresponders to IFN α-2 Therapy

- Re-treat with more aggressive/effective treatment?
- Place on maintenance therapy?
- Wait for future agents to be developed?

Treatment options: nonresponders

- No FDA-approved treatments.
- Combination therapy
- Maintainence Interferon Treatment
  - May decrease late complications of hepatitis
  - Several ongoing studies
- Discontinuation of therapy

Goals of Therapy

- Primary Goal: Eradicate HCV Infection

Treatment Options for Alpha 2 Interferon Nonresponders

<table>
<thead>
<tr>
<th>Primary Goal</th>
<th>Secondary Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiviral Strategy</td>
<td>Hepatitis Histology Strategy</td>
</tr>
<tr>
<td>• Alpha 2 high-dose retreatment</td>
<td></td>
</tr>
<tr>
<td>• More effective interferons</td>
<td></td>
</tr>
<tr>
<td>• Future therapies</td>
<td></td>
</tr>
<tr>
<td>• Maintenance therapy</td>
<td></td>
</tr>
<tr>
<td>• Future therapies</td>
<td></td>
</tr>
</tbody>
</table>
Change in Fibrosis Stage 3 Years After Study Entry

- Untreated patients
- No SVR
- IFN-treated
- SVR

Retreatment of Alpha 2 IFN Monotherapy Relapsers and Nonresponders

SVR in Alpha 2 IFN Monotherapy Relapsers and Nonresponders

SVR in Alpha 2 IFN Relapsers


Studies of Retreatment in Alpha 2 IFN Monotherapy Nonresponders

IFN-α 2b (Intron-A®)

Previously failed 3 MU x 6 months
- Puoti 1996 (6-3 MU x 12 months) 0%
- Giudici 1996 (3-6 MU x 12-24 months) 3%
- Chemello 1997 (6 MU x 12 months) 0%
- Chow 1998 (5 MU x 12 months) 0%

Consensus Interferon
- Heathcote 1998 (15 mcg x 12 months) 13%

Future Disease Burden: 2008

Estimated Increase by the Year 2008

Future Disease Burden: 2008

Estimated Increase by the Year 2008

Growing Number of Nonresponders to Alpha 2 Interferons

Patients (thousands)

Actively treated
Nonresponder pool

HEPATITIS C VIRUS

Genome

RNA dependent RNA polymerase
Protein Targets for Specific HCV Antiviral Therapy

HCV polyprotein

NS3 protease domain
NS3 helicase domain
NS3/NS4 bifunctional protease/helicase
NS5B RNA-dependent RNA polymerase

NS2/3 metalloprotease Binds PKR

Timelines for FDA New Drug Approval

Pre-Clinical Phase I-II Phase II-III Phase III-Market FDA Approval
0% 100% 71% 32% 21% 21%
1 Year 3 Years 3 Years 1 Year

Company | Product | Status | Description
--- | --- | --- | ---
Anadyr | ANA245 | Ph. I | Nucleoside
Boehringer | BrE N2061 | Adv. | Protease inhibitor
Chiron/ESC | HCV Vaccine | Ph. I | Vaccine
Human Genome | Alulilcon | Ph. III | Fusion inhibitor + IFN
IDSA | Transferase IFN | Ph. I | Transferase + IFN
Roche/Pharmacia | Levovirin | Ph. I | Gln for ribavirin
Merck | NM283 | Ph. II | Polymerase inhibitor
Amgen | IFN alfa | Ph. II | Oral formulation
BioMedicines | Omega IFN | Ph. II | IFN omega
Imugenetics | HCOVE-1 vaccine | Ph. II | HCV E1 protein
InterMune | Actimmune | Ph. II | Antibiotic
Inovio | Peg-interferon | Ph. II | Pegylated consensus IFN
iba | IBS 1403 | Ph. II | Antiviral targeting RES
Macom | Captopir | Ph. II | Antiviral immune modulator
Ribapharm | Viramidine | Ph. II | Ribavirin prodrug
Viragen | Multiferon | Ph. II | Multitype human IFN