بسم الله الرحمن الرحيم

قالوا سبحانه لا علم لنا إلا ما علمتنا إبنك إبن العالم الحكيم

سورة البقرة: الآية 187
HCV RELAPSERS AND NONRESPONDERS:
How to deal with them?

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Achieving SVR

The ability to achieve a SVR is the result of 3 independent steps

- The patient must achieve a virologic response
- The patient must maintain the response
- The patient must not relapse

To overcome nonresponse and relapse, the reasons for failure must be defined
Defining an Initial Virologic Response
Chronic Hepatitis C: Defining an Initial Virologic Response

- **PegIFN/RBV**
- **Null response**
- **Partial response**
- **Breakthrough**
- **Relapse**
- **2 log decline**
- **Limit of detection**
- **SVR**

**HCV RNA (log_{10} IU/mL)**

**Weeks**

0 4 8 12 18 24 30 36 42 48 54 60 66 72 78
Frequency of Responses

- EVR = 80%

Medical Need in Chronic Hepatitis C Retreatment Is Growing

Despite significant advances in HCV therapy, approximately half of genotypes 1 and 4 patients do not achieve SVR on initial treatment.

First generation HCV oral direct antivirals are several years from approval

Initial Approach to the Patient With Treatment Failure

• Review of records to assess status of previous response to therapy
  – End-of-treatment HCV RNA level critically important
  – Duration of previous treatment
  – Degree of HCV RNA reduction as a result of previous therapy

• Determination of previous degree of compliance
  – Which interferon alfa regimen was taken and at which dose?
  – How many ribavirin tablets/day at starting dose?
  – How many missed doses?
  – How many dose reductions?
  – May have to ask patients repeatedly to get accurate answers
Populations of Nonresponders

- IFN Monotherapy
- IFN and RBV
- PegIFN and RBV
Why Patients Fail HCV Therapy

- Noncompliance with physician recommendations
- Inherently resistant to IFN
- Response not recognized
- Adverse events
  - Therapy stopped
  - Dose of pegIFN and/or RBV reduced
- Treatment not continued for a sufficient period of time
Treatment of Chronic Hepatitis C: Impact of Stopping RBV

- Those who stopped RBV at Wk 24 had higher breakthrough and relapse rates.
Why Patients Fail HCV Therapy

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- Inherently resistant to IFN
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- Adverse events
  - Therapy stopped
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The Null Response

- No significant decline in HCV RNA despite full-dose pegIFN
- Occurs in 20% of patients
- Patients likely resistant to the effects of IFN
- Pattern more common in blacks
- May not be overcome by higher doses of pegIFN?
Why Patients Fail HCV Therapy

- Noncompliance with physician recommendations
- Inherently resistant to IFN
- Response not recognized
- Adverse events
  - Therapy stopped
  - Dose of pegIFN and/or RBV reduced
- Treatment not continued for a sufficient period of time
• HCV RNA should be measured at monthly intervals until the patient either has undetectable HCV RNA or a nonresponse pattern has been defined and treatment is discontinued.

Once undetectable, it is recommended that HCV RNA be monitored every 3 months until 24 weeks after treatment is discontinued.
Why Patients Fail HCV Therapy

- Noncompliance with physician recommendations
- Inherently resistant to IFN
- Response not recognized
- Adverse events
  - Therapy stopped
  - Reduced dose of pegIFN and/or RBV
  - Treatment not continued for a sufficient period of time
Adjusting Dose—Do Not Stop

<table>
<thead>
<tr>
<th>Hb (g/dL)</th>
<th>HCV RNA (log_{10} IU/mL)</th>
<th>RBV Dose (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>36</td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>42</td>
<td></td>
<td>48</td>
</tr>
</tbody>
</table>

Weeks: 0 4 8 12 18 24 30 36 42 48
It is difficult for many patients to tolerate even the standard duration of peginterferon alfa and ribavirin therapy.

Many studies have suggested that at least 20% of patients have adverse events that are severe enough to require either a reduction in the dose of peginterferon alfa and/or ribavirin, a temporary treatment interruption, or a permanent discontinuation of treatment.
Neither peginterferon alfa nor ribavirin dosing should be interrupted unless the adverse event is particularly severe and there is a concern for patient safety.
Impact of RBV Dose after 12 Weeks

- Patients received > 97% of RBV during Weeks 1-12
- Completed all 48 weeks of treatment
- Any reduction in RBV dose occurred after Week 12

Peginterferon α<sub>2b</sub> + Ribavirin
Sustained Virologic Response by Weight

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>3 MIU + ribavirin 1,000 mg-1,200 mg</th>
<th>PEG 0.5 µg/kg + Ribavirin 1,000 mg-1,200 mg</th>
<th>PEG 1.5 µg/kg + Ribavirin 800 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 kg</td>
<td>57%</td>
<td>47%</td>
<td>62%</td>
</tr>
<tr>
<td>65-85 kg</td>
<td>48%</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>&gt;85 kg</td>
<td>41%</td>
<td>46%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Schering Corporation, data on file
Manns et al., Lancet 2001
Why Patients Fail HCV Therapy

- Noncompliance with physician recommendations
- Inherently resistant to IFN
- Response not recognized
- Adverse events
  - Therapy stopped
  - Dose of pegIFN and/or RBV reduced
- Treatment not continued for a sufficient period of time
Adherence to therapy

Patients achieving the 80/80/80 adherence goal:

- Taking 80% of the interferon dose
- And 80% of the ribavirin dose
- For 80% of the expected duration of therapy.
Why Retreat?
Two Schools of Thought: Retreat Now vs. Wait for Newer Agents Before Retreating

**RETREAT NOW**
- Eradicate virus
- Stop or reverse fibrosis
- Decrease risk of HCC

**WAIT TO RETREAT**
- Concerns about efficacy
- Side effects of therapy
- New antivirals coming soon
Who Can Benefit from Retreatment?
When Considering Retreatment, Results from Small-Scale Studies Using PEG-IFN alfa-2b Aid Patient Selection

<table>
<thead>
<tr>
<th>Factor</th>
<th>Study Parameters</th>
<th>Impact on Retreatment SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Treatment Response (Relapser vs. Nonresponder)</td>
<td>N=152 (Relapsers=46; N/R=95). 48 wks of treatment</td>
<td>Relapsers more likely to achieve retreatment SVR¹</td>
</tr>
<tr>
<td>Genotype</td>
<td>N=182 (G1=87%). 48 wks of treatment</td>
<td>Genotype 2 and 3 are more likely to achieve retreatment SVR²</td>
</tr>
<tr>
<td>Retreatment Baseline Viral Load</td>
<td>N=141 (52%=HVL). 48 wks of treatment</td>
<td>Baseline low viral load more likely to achieve retreatment SVR³</td>
</tr>
</tbody>
</table>
How Should We Approach Retreatment?
Management Strategies

- Increase induction dose of pegIFN + weight-based RBV
- Initiate treatment with albumin IFN + weight-based RBV
- Low-dose pegIFN to manage sequelae
- Watch and wait
Options in PegIFN + RBV

Nonresponders

- Retreat in the event of poor adherence to previous therapy
- Longer course of treatment for relapsers
  - Extrapolation of 48- vs 72-wk results in slow responders
- Other IFNs (consensus IFN, albumin IFN)
- Maintenance therapy
- Clinical trials of new agents
- “Watching and waiting”: an option not to be ignored
Partial Responder: Impact of Intensifying Therapy

HCV RNA ($\log_{10}$ IU/mL) vs. Weeks

- **Partial response**
- **Limit of detection**
- **2 log decline**

**PegIFN/RBV**
Partial Responder: Impact of Intensifying Therapy (cont’d)

- HCV RNA (log_{10} IU/mL)
- 0 4 8 12 18 24 30 36 42 48 54 60 66 72 78
- PegIFN/RBV
- Intensify PegIFN dose
- 2 log decline
- Limit of detection
- SVR
Slow-to-Respond Patients: Extending Therapy

HALT-C: Retreatment of Standard IFN Nonresponders With PegIFN + RBV

- PegIFN alfa-2a 180 μg/wk + RBV 1000-1200 mg/day
- Patients with bridging fibrosis or cirrhosis included
- If viral clearance achieved at 20 wks → continue treatment through 48 wks

RENEW: Higher-Dose PegIFN alfa-2b Increases SVR Rate

IFN + RBV Nonresponders* Treated With RBV 800-1400 mg/day and PegIFN α-2b 1.5 µg/kg or 3.0 µg/kg for 48 Wks (N = 704)

SVR (%)

P = .03

12
17

1.5 µg/kg/wk (n = 352)
3.0 µg/kg/wk (n = 352)

*91% genotype 1.

REPEAT: No Benefit Associated With High-Dose Induction

Extended treatment did not increase ETR but did decrease relapse

*Patients randomized who received at least one dose of study medication

Testing a Stringent Week 12 Stopping Rule with PEG-IFN alfa-2b: EPIC³ Retreatment Study Design

Patients enrolled on or before April 1, 2004  
\( n = 1354 \)

Efficacy population  
\( n = 1336 \)

12 Weeks*

- **HCV RNA undetectable**  
  \( n = 499 \)

- **HCV RNA Positive with \( \geq 2 \) log drop in HCV RNA**  
  \( n = 293 \)

- **HCV RNA Positive with \( < 2 \) log drop in HCV RNA**  
  \( n = 457 \)

\( n = 143 \dagger \)

- Completed 48 weeks of therapy and 24-week follow-up  
  \( n = 650 \)

- Entered maintenance protocols or discontinued  
  \( n = 599 \)

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*87 patients did not have 12-week data; 1 missing baseline HCV RNA  
**LLD < 125 IU/mL  
†Continued in the protocol at the discretion of the investigator  
Efficacy Results Overall by Prior Treatment

Proportion of Patients Achieving SVR
PegIntron® (1.5 µg/kg/w) + Ribavirin (800-1400 mg/d), 48 weeks

- **Overall**: 23%
  - **n = 1336**
- **Prior IFN + RBV**: 25%
  - **n = 1030**
- **Prior PEG-IFN + RBV**: 16%
  - **n = 299**

Poynard T, et al. HepDART 2007, Poster 110. PegIntron SmPC
Whether Prior Therapy Was with Pegylated or Non-Pegylated IFN, Prior Relapsers More Likely to Achieve Retreatment SVR

Proportion of Patients Achieving SVR
PegIntron® (1.5 µg/kg/w) + Ribavirin (800-1400 mg/d), 48 weeks

- **Overall**: n = 1336
  - Nonresponder: 15%
  - Relapser: 41%
  - Treatment Failure: 28%
- **Prior IFN + RBV**: n = 1030
  - Nonresponder: 17%
  - Relapser: 45%
  - Treatment Failure: 30%
- **Prior PEG-IFN + RBV**: n = 299
  - Nonresponder: 4%
  - Relapser: 36%
  - Treatment Failure: 7%

Schering-Plough. Data on File
Overall, Relapsers Were More Likely to Achieve Viral Negativity at Treatment Week 12

Proportion of Patients Achieving EVR as a Function of Prior Virologic Response

PegIntron® (1.5 µg/kg/w) + Ribavirin (800-1400 mg/d), 48 weeks

- Prior Relapsers: 66%
- Prior Nonresponders: 25%
- Prior Treatment Failures: 43%

Schering-Plough Data on File.
The Week 12 Response Is Highly Predictive of SVR Regardless of Genotype

Proportion of Patients Achieving SVR
PegIntron® (1.5 µg/kg/w) + Ribavirin (800-1400 mg/d), 48 weeks

% Patients

Overall
Undetectable HCV RNA
Detectable HCV RNA
But >2 log decrease

G1: 16% 57% 74%
G2: 10% 48% 72%
G3: 20% 60% 60%
G4: 30% 5% 0%

The New Week 12 Retreatment Milestone
Derived from EPIC³ Response Analyses

- **HCV RNA Week 12**
  - **Detectable**
    - Consider Stopping Treatment
  - **Undetectable**
    - Continue Treatment for 48 Weeks

- EPIC³ data establish a Week 12 decision point for continuing retreatment with PEG-IFN + RBV
- Patients with undetectable HCV RNA at Week 12 have a >50% chance of attaining an SVR
- For those with detectable HCV RNA at Week 12, the odds of attaining an SVR are low
Depending on the reasons for initial failure, many patients are likely to achieve SVR with a second course of treatment.

In the EPIC\(^3\) study, SVR was attained by 23% of patients overall.

Among those who were negative at week 12:
- 57% achieved SVR: 59% of prior non-pegylated failures and 47% of prior pegylated failures.

Applying a stringent week 12 stopping rule can be a powerful motivator to encourage patients toward another course of treatment.
Novel Agents in Development
DIRECT: cIFN 9 µg vs 15 µg + RBV in PegIFN/RBV Nonresponders

Modified ITT*  

Patients with at least 12 wks of viral negativity after end of treatment; RBV dosed at 1000-1200 mg/day.

DIRECT: Summary

• Patients with lower fibrosis stages experienced improved responses with cIFN
• Noncirrhotic patients with greater HCV RNA reductions during previous pegIFN/RBV therapy had the best response
• 15 µg cIFN group consistently experienced a better response than the 9 µg cIFN group
• cIFN/RBV had an acceptable tolerability profile at doses up to 15 µg

Boceprevir + PegIFN/RBV: Phase II Nonresponder Study, GT 1

- Response dependent on interferon responsiveness

Patients With Detectable HCV RNA or < 2 log_{10} Decline in HCV RNA at ≥ 12 Wks of Previous PegIFN + RBV (N = 357)

SVR (%)

- PegIFN α-2b + RBV
- Boceprevir* + PegIFN α-2b + RBV (Various Arms)

*100, 200, 400, and 800 mg TID boceprevir.

Conclusion: Management of PegIFN + RBV Nonresponders

- Consider longer duration of retreatment in relapsers
- Potential benefit of pegIFN alfa-2a/b crossover concept still to be proven
- Optimize weight-based RBV dose in retreated patients
- Higher doses of pegIFN alfa may be superior to standard dose in selected patients
Conclusion: Management of PegIFN + RBV Nonresponders

• Potential role for cIFN in selected patients (eg, partial responders, noncirrhotics, relapsers)
• Longer treatment durations in nonresponders should be considered, depending on viral kinetics, tolerability, degree of fibrosis
• Maintenance therapy of uncertain efficacy
• Watch and wait approach is reasonable in many patients
Thank you