HOW TO USE TRIPLE THERAPY FOR GENOTYPE1 HCV INFECTION

14:00-15:30

Hall 5

14:20

HCW3-02

Monitoring and Stopping Rules

M. Ghany, USA
Monitoring And Stopping Rules

Marc G. Ghany, MD, MHSc
Liver Diseases Branch, NIDDK, NIH
Bethesda, MD
Why Do We Monitor?

- Assess response to therapy
- Determine duration of therapy
- Apply stopping rules
- Detect emergence of antiviral resistance
- Assess treatment safety
Assessing Response To Therapy

• **ALT: Biochemical response**
  – Normalization of ALT

• **Liver biopsy: Histological response**
  – 2 point decrease in necroinflammation with no worsening in fibrosis

• **HCV RNA: Virological response**
  – HCV RNA undetectable
Monitoring Treatment Efficacy

Baseline

- **Response**
  - RVR
  - cEVR
  - pEVR

- **Non-response**
  - Partial response
  - Null response
  - Breakthrough

On-Treatment

- **Response**
  - RVR
  - cEVR
  - pEVR

Post-Treatment

- **Response**
  - SVR
  - **Non-response**
  - Relapse

Weeks:

- Before: Baseline
- During: Week 4, Week 12
- After: Week 24 or 48, Week 48 or 72
SVR 12 is Equivalent to SVR 24

<table>
<thead>
<tr>
<th>SVR 4 Assessment</th>
<th>‘Y’</th>
<th>‘N’</th>
<th>PPV: 91.1%</th>
<th>NPV: 98.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Y’</td>
<td>4239</td>
<td>412</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘N’</td>
<td>53</td>
<td>3002</td>
<td></td>
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</table>

Sensitivity: 98.7%
Specificity: 87.7%

<table>
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<tr>
<th>SVR 12 Assessment</th>
<th>‘Y’</th>
<th>‘N’</th>
<th>PPV: 98%</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Y’</td>
<td>5428</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>‘N’</td>
<td>56</td>
<td>4617</td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity: 99%
Specificity: 98.0%

• ~2% of patients with SVR12 relapse by SVR24 assessment (false positive)

• Less agreement between SVR4 and SVR24

Slide courtesy Russell Fleisher FDA
Assays For Monitoring HCV RNA

- Roche
- Abbott
- Siemens
- NGI

Log HCV RNA IU/mL

Dynamic Range

LOD
Type of HCV RNA Assay Matters

• An HCV assay with:
  – a lower limit of quantification of $\leq 25$ IU/mL
  – Lower limit of detection of $\sim 10^{-15}$ IU/mL

• Should be used for:
  – Monitoring response to therapy
  – Decision making during triple therapy
BOC Trial: Detectable/BLOQ Is Not Equal To Target Not Detected And Is Associated with a Lower SVR Rate

TVR Trial: Detectable/BLOQ Is Not Equal To Target Not Detected And Is Associated with a Lower SVR Rate

*T12/PR48*

<table>
<thead>
<tr>
<th>% SVR</th>
<th>WK4</th>
<th>WK8</th>
<th>WK10</th>
<th>WK12</th>
<th>WK16</th>
<th>WK20</th>
</tr>
</thead>
</table>

- Undetectable
- Detectable/BLOQ
- Quantifiable (≥25)

Why Do We Monitor?

- Assess response to therapy
- **Determine duration of therapy**
- Apply stopping rules
- Detect emergence of antiviral resistance
- Assess treatment safety
FDA Approved Regimen with BOC + PegIFN/RBV in Rx-Naïve, no cirrhosis

Rapid response
HCV RNA undetectable weeks 8-24

Slow response
HCV RNA detectable week 8, undetectable week 24

PegIFN & RBV & BOC

PegIFN & RBV
FDA Approved Regimen With TVR + PegIFN/RBV in Treatment-Naïve Patients, without Cirrhosis

- HCV RNA undetectable weeks 4 & 12
- HCV RNA detectable week 4 and/or 12

PegIFN & RBV

PegIFN & RBV & TVR

0 4 12 24 48
RVR: Treat for 24 weeks

HCV RNA (log_{10} IU/mL)

Weeks

PegIFN/RBV

RVR

SVR

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

0 1 2 3 4 5 6 7 8
EVR: Treat for 48 weeks

EVR: Treated for 48 weeks

Weeks

HCV RNA (log_{10} IU/mL)

PegIFN/RBV

RVR

EVR

SVR

decline
Slow Virological Response: Treat for 72 weeks

- **HCV RNA (log_{10} IU/mL)**
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8

- **Weeks from start of treatment**
  - 0
  - 4
  - 8
  - 12
  - 18
  - 24
  - 30
  - 36
  - 42
  - 48
  - 54
  - 60
  - 66
  - 72
  - 80
  - 96

- **PegIFN/RBV treatment period**

- **RVR**
- **EVR**
- **Slow response**
- **SVR**
Why Do We Monitor?

• Assess response to therapy
• Determine duration of therapy
• Apply stopping rules
• Detect emergence of antiviral resistance
• Assess treatment safety
Stopping Rules

- Limit exposure to therapy with significant toxicity
- Lessen emergence of antiviral resistance
Peginteron and Ribavirin

Stopping Rules
- HCV RNA ≤ 2 Log change from baseline
- HCV RNA detectable

Weeks: 0, 4, 12, 24, 48
FDA Approved Regimen with BOC + PegIFN/RBV in Rx-Naïve, no cirrhosis

Rapid response: HCV RNA undetectable weeks 8-24

Slow response: HCV RNA detectable week 8, undetectable week 24

Stopping Rules:
- Stopping when HCV RNA ≥ 100 IU/ml
- Stopping when HCV RNA detectable

Regimen:
- PegIFN & RBV & BOC
- PegIFN & RBV

Timeline:
- 0 week
- 4 week
- 8 week
- 12 week
- 24 week
- 28 week
- 36 week
- 48 week
FDA Approved Regimen With TVR + PegIFN/RBV in Treatment-Naïve Patients, without Cirrhosis

Stopping Rules

- HCV RNA undetectable weeks 4 & 12
- PegIFN & RBV

PegIFN & RBV & TVR

HCV RNA detectable week 4 and/or 12

- PegIFN & RBV

0 4 12 24 48 weeks

HCV RNA > 1,000 IU/ml

HCV RNA detectable
Why Do We Monitor?

- Assess response to therapy
- Determine duration of therapy
- Apply stopping rules
- Detect emergence of antiviral resistance
- Assess treatment safety
Virological Breakthrough

Log HCV RNA

Antiviral Agent

Viral rebound

Virologic breakthrough

Genotypic resistance

Time

1 log*
Monitoring Viral Load Is Also Predictive Of Development Of Resistance

Jacobson IM, et al. NEJM 2011;364:2405
Why Do We Monitor?

- Assess response to therapy
- Determine duration of therapy
- Apply stopping rules
- Detect emergence of antiviral resistance
- Assess treatment safety
Side effects of IFN therapy

Early side effects
- Fatigue
- Fever
- Chills
- Myalgias
- Arthralgias
- Backache
- Headache
- Anorexia
- Nausea
- Diarrhea
- Impaired concentration
- Difficulty sleeping

Late side effects
- Fatigue
- Low-grade fever
- Chills
- Myalgias
- Backache
- Headache
- Anorexia
- Weight loss
- Difficulty sleeping
- Increased need for sleep
- Decreased libido
- Hair loss
<table>
<thead>
<tr>
<th>Side effects of IFN therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
</tr>
<tr>
<td>• Bone marrow suppression</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
</tr>
<tr>
<td>• Urinary tract infection</td>
</tr>
<tr>
<td>• Sinusitis</td>
</tr>
<tr>
<td>• Bronchitis</td>
</tr>
<tr>
<td>• Septicemia</td>
</tr>
<tr>
<td>• Lung abscess</td>
</tr>
<tr>
<td>• Brain abscess</td>
</tr>
<tr>
<td>• Bacterial periton</td>
</tr>
<tr>
<td><strong>Autoimmune</strong></td>
</tr>
<tr>
<td>• Autoantibody formation</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
</tr>
<tr>
<td>• Hyperthyroidism</td>
</tr>
<tr>
<td>• Other autoimmune disease</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
</tr>
<tr>
<td>• Irritability</td>
</tr>
<tr>
<td>• Anxiety</td>
</tr>
<tr>
<td>• Loss of interest</td>
</tr>
<tr>
<td>• Social withdrawal</td>
</tr>
<tr>
<td>• Depression</td>
</tr>
<tr>
<td>• Delerium</td>
</tr>
<tr>
<td>• Disorientation</td>
</tr>
<tr>
<td>• Clouding of consciousness</td>
</tr>
<tr>
<td>• Suicidal ideation</td>
</tr>
<tr>
<td>• Paranoid ideation</td>
</tr>
<tr>
<td>• Return of craving for drugs and alcohol</td>
</tr>
<tr>
<td>• Accentuation of previous symptoms, such as phobias, obsessional thoughts, rituals</td>
</tr>
</tbody>
</table>
Side Effects of Ribavirin

- Hemolytic anemia
- Lymphopenia
- Hyperuricemia
- Itching
- Rash
- Cough
- Nasal stuffiness
Frequency of Discontinuation and Dose Reduction With PegIFN & RBV

<table>
<thead>
<tr>
<th></th>
<th>Discontinuation</th>
<th>Dose reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFN &amp; RBV</td>
<td>10-14%</td>
<td>18-20%</td>
</tr>
<tr>
<td></td>
<td>Neutropenia (ANC &lt;1500 mm³)</td>
<td>Anemia (Hgb &lt;10 g/dL)</td>
</tr>
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Ghany MG et al Hepatology 2009;49:13351374
BOC Plus PegIFN alfa-2b/RBV: Adverse Events

- Higher rates of anemia, neutropenia, and dysgeusia in BOC arms vs control

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>PR48 (n = 467)</th>
<th>BOC + PR RGT/48* (n = 1225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia*</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>16</td>
<td>35</td>
</tr>
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TVR Plus PegIFN alfa-2a/RBV: Adverse Events

- Higher rates of rash, anemia, and anorectal signs and symptoms in TVR arms vs control

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>PR48 (n = 493)</th>
<th>TVR + PR RGT/48*† (n = 1797)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>34</td>
<td>56</td>
</tr>
<tr>
<td>Anemia‡</td>
<td>17</td>
<td>36</td>
</tr>
<tr>
<td>Anorectal events</td>
<td>7</td>
<td>29</td>
</tr>
</tbody>
</table>

- In most subjects, rash was mild to moderate
  - Severe rash in 4%; discontinuation due to rash in 6% of subjects

Safety Concerns Increased in Patients With More Advanced Disease

• CUPIC trial: early access program with telaprevir and boceprevir from France enrolling treatment-experienced patients with cirrhosis
  – Wk 16 interim analysis of 497 patients
• High rate of serious adverse events: 33% to 45%
• High rate of anemia
  – Grade 2: 19% to 23%
  – Grade 3/4: 4% to 12%
• High rate of premature discontinuation: 23% to 26%

### Monitoring Schedule During Therapy With PegIFN and RBV

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Recommended Tests</th>
<th>Rationale</th>
</tr>
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<tbody>
<tr>
<td>Before starting therapy</td>
<td>CBC, hepatic panel, TSH, quantitative HCV RNA, genotype, ANA pregnancy test for women of child-bearing age</td>
<td>Assess candidacy for treatment</td>
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<tr>
<td>Week 4</td>
<td>CBC, hepatic panel, consider quantitative HCV RNA</td>
<td>Assess rapid virologic response and cytopenia</td>
</tr>
<tr>
<td>Week 12</td>
<td>CBC, hepatic panel, quantitative HCV RNA, TSH</td>
<td>Assess early virologic response (early stopping rule), monitor cytopenia and thyroid dysfunction</td>
</tr>
<tr>
<td>Week 24 Or 48</td>
<td>CBC, hepatic panel, TSH, quantitative HCV RNA</td>
<td>Assess response (futility stopping rule), thyroid dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assess end of treatment response</td>
</tr>
<tr>
<td>Week 48 or 72</td>
<td>CBC, hepatic panel, Qualitative HCV RNA</td>
<td>Assess SVR and resolution of cytopenia</td>
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## Monitoring Schedule During Therapy With Triple Therapy

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<tr>
<td>Week 2, 4, 8 and q 4 weeks</td>
<td>CBC, LFTs, quantitative HCV RNA</td>
<td>Assess rapid virologic response and cytopenia</td>
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<td>CBC, hepatic panel, quantitative HCV RNA, TSH</td>
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Take Home Messages

• A real-time PCR-based assay with a lower limit of detection of 10-15 IU/ml should be used for monitoring HCV RNA level
• Monitoring HCV RNA level is important for:
  – Assessing response to therapy
  – Determining duration of therapy and stopping treatment for futility
  – Detecting emergence of antiviral resistance
• Important to monitor for side effects to ensure adequate safety of treatment