Update in the Management of Hepatitis C: What Does the Future Hold

Paul Y. Kwo, MD, FACG
Professor of Medicine
Medical Director, Liver Transplantation
Gastroenterology/Hepatology Division
Indiana University School of Medicine
975 W. Walnut, IB 327
Indianapolis, IN 46202-5121
phone 317-274-3090
fax 317-274-3106
email pkwo@iu.edu

The components of treatment in HCV infection

- PEG IFN
- NS5b
- NS3
- NS5a
- RBV
- NNI
**Direct-Acting Antiviral Agents (DAAs) - Key Characteristics**

- **NS3 /4A Inhibitors (Protease inhibitor PI)**
  - High potency
  - Limited genotypic coverage
  - Low barrier to resistance

- **NS5B Nucleos(t)ide Inhibitors (NI)**
  - Intermediate potency
  - Pan genotypic coverage
  - High barrier to resistance

- **NS5A Inhibitors**
  - High potency
  - Multi-genotypic coverage
  - Low barrier to resistance

- **NS5B Non Nucleoside Inhibitors (NNI)**
  - Intermediate potency
  - Limited genotypic coverage
  - Low barrier to resistance

**Genotype 1 Treatment-Naive Patients**

- **Interferon eligible**
  - Sofosbuvir (400 mg) and weight-based RBV (1000-1200 mg) plus weekly PEG for 12 weeks regardless of subtype (1a or 1b)
    - Alternative Regimen: simeprevir (150 mg) for 12 weeks and weight-based RBV (1000-1200 mg) plus weekly PEG for 24 weeks for genotype 1b or genotype 1a infection in without Q80 polymorphism

- **Patients who are NOT eligible to receive IFN:**
  - Sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000-1200 mg) for 12 weeks regardless of subtype (1a or 1b)
    - Daily sofosbuvir (400 mg) and weight-based RBV (1000-1200 mg) regardless of subtype
The current standard of care: Genotype 1 patients who have failed therapy

- Patients who failed therapy without protease inhibitor regardless of IFN eligibility
  - Sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000-1200 mg) for 12 weeks regardless of subtype (1a or 1b)
    - Alternative Regimen: simeprevir (150 mg) for 12 weeks and weight-based RBV (1000-1200 mg) plus weekly PEG for 48 weeks regardless of subtype (1a or 1b), no Q80K testing
    - Alternative Regimen including those who have failed protease inhibitor: and can tolerate IFN: Sofosbuvir (400 mg) and weight-based RBV (1000-1200 mg) plus weekly PEG for 12-24 weeks regardless of subtype (1a or 1b)

NEUTRINO Study:
SVR12 by HCV Genotype

![Graph showing SVR12 by HCV Genotype](image-url)

Error bars represent 95% confidence intervals.
Lawitz E, et al. 48th EASL; Amsterdam, Netherlands; April 24-28, 2013. Abst. 1411.
The components of SVR in HCV with nucleotide polymerase inhibitor + NS5a for genotype 1
Sofosbuvir 400 mg/Ledipasvir 90 mg approved for genotype 1 infection 10/10/14

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommended Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve with or without cirrhosis</td>
<td>12 weeks*</td>
</tr>
<tr>
<td>Treatment-experienced** without cirrhosis</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment-experienced** with cirrhosis</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

* SOF/LDV for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/ml.
** Treatment-experienced patients who have failed treatment with either peginterferon alfa + ribavirin or an HCV protease inhibitor + peginterferon alfa + ribavirin.

Study Design
GT 1 Treatment-Naïve (ION-1)

- GT 1 HCV treatment-naïve patients in Europe and USA
- Broad inclusion criteria
  - Targeted 20% enrollment of patients with cirrhosis
  - No upper age or BMI limit
  - Platelet count ≥50,000/mm³, no neutrophil minimum
- 865 patients randomized 1:1:1:1 across four arms
- Stratified by HCV subtype (1a or 1b) and cirrhosis
SVR12: Absence of Cirrhosis vs Cirrhosis
GT 1 Treatment-Naïve (ION-1)

Error bars represent 95% confidence intervals.

179/180
178/184
181/184
179/181

32/34
33/33
31/33
36/36

12 Weeks
24 Weeks

LDV/SOF
LDV/SOF + RBV
LDV/SOF
LDV/SOF + RBV

GT 1 Treatment-Naïve (ION-3): 8 weeks of therapy with SOD/LDV leads to high SVR rates in non-cirrhotic naïve patients

- GT 1 treatment-naïve patients without cirrhosis
- Broad inclusion criteria
  - No upper age or BMI limit
  - Opiate substitution therapy allowed
- 647 patients randomized 1:1:1 across three arms
- Stratified by HCV subtype (1a or 1b)
ION 3: SVR12 With 8 or 12 Wks SOF/LDV ± RBV in Tx-Naive Non-cirrhotic Patients

Post hoc analysis notes high SVR rates in those with HCV RNA < 6 X 10^6 IU/ml

<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>SVR (%) with Baseline HCV RNA &lt; 6 million IU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 wks</td>
<td>87 (119/123)</td>
</tr>
<tr>
<td>12 wks</td>
<td>86 (126/131)</td>
</tr>
</tbody>
</table>

SVR12 rates did not differ by GT1a vs GT1b in any treatment arm

Virologic failure: 23 relapses (11 in 8-wk SOF/LDV, 9 in 8-wk SOF/LDV/RBV, 3 in 12-wk SOF/LDV)

GT 1 Treatment-Experienced (ION-2): Study Design

- GT 1 HCV patients who had failed prior IFN-based therapy, including regimens containing a NS3/4A protease inhibitor
- Broad inclusion criteria
  - Targeted 20% enrollment of patients with cirrhosis
  - No upper age or BMI limit
  - Platelet count ≥ 50,000/mm^3, no neutrophil minimum
- 440 patients randomized 1:1:1:1 across four arms
- Stratified by HCV subtype (1a or 1b), cirrhosis, prior treatment response
ION 2: SVR12 With 12 or 24 Wks of SOF/LDV ± RBV by Cirrhosis Status

24 weeks duration for cirrhosis patients

- SVR12 rates were significantly lower in cirrhotic vs noncirrhotic patients in the pooled 12-wk arms
- Previous treatment with protease inhibitor or did not matter


The components of SVR in HCV:
High SVR rates without a nucleotide polymerase inhibitor coming soon

NS3
NS5b
NNI
NS5a
RBV
Paritaprevir/ RTV Ombitasvir + Dasabuvir + RBV in HCV Genotype 1 (SAPPHIRE-I):

Phase 3 Study
Double-Blind

Key eligibility criteria
- HCV genotype 1
- Treatment-naive
- No cirrhosis
- No HIV or HBV

Paritaprevir/ RTV (150/100 mg) co-formulated with Ombitasvir (25 mg) and administered once-daily. Dasabuvir (250 mg) + RBV (weight-based dosing) administered twice-daily.

*After week 12, placebo patients received open-label Paritaprevir/ RTV Ombitasvir + Dasabuvir + RBV for 12 weeks.
Primary outcome: SVR12.

SAPPHIRE-I Results:
ITT SVR12 Rates

<table>
<thead>
<tr>
<th></th>
<th>% Patients</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>96.2%</td>
<td>455/473</td>
</tr>
<tr>
<td>GT1a</td>
<td>95.3%</td>
<td>307/322</td>
</tr>
<tr>
<td>GT1b</td>
<td>98.0%</td>
<td>148/151</td>
</tr>
</tbody>
</table>

Feld JJ, et al. NEJM 2014; 370:1594-603
Paritaprevir/ RTV Ombitasvir + Dasabuvir ± RBV in GT1 Patients Without Cirrhosis: Is RBV Necessary? (PEARL III and PEARL IV)

**PEARL III**
- DAA-naive pts with GT1a HCV (N = 305)
  - PTV/RTV/OMB + DBV + placebo (n = 205)
  - PTV/RTV/OMB + DBV + RBV (n = 100)
- SVR12, %:
  - Wk 12: 97
  - Wk 24: 90

**PEARL IV**
- DAA-naive pts with GT1b HCV (N = 419)
  - PTV/RTV/OMB + DBV + placebo (n = 210)
  - PTV/RTV/OMB + DBV + RBV (n = 209)
- SVR12, %:
  - Wk 12: 99.5
  - Wk 24: 99

**PEARL III**
- DAA-naive pts with GT1a HCV (N = 305)
  - PTV/RTV/OMB + DBV + placebo (n = 205)
  - PTV/RTV/OMB + DBV + RBV (n = 100)
- SVR12, %:
  - Wk 12: 97
  - Wk 24: 90

**PEARL IV**
- DAA-naive pts with GT1b HCV (N = 419)
  - PTV/RTV/OMB + DBV + placebo (n = 210)
  - PTV/RTV/OMB + DBV + RBV (n = 209)
- SVR12, %:
  - Wk 12: 99.5
  - Wk 24: 99


**Paritaprevir/ RTV Ombitasvir + Dasabuvir + RBV in HCV Genotype 1 non-responders (SAPPHIRE-II):**

**Phase 3 Study**
- Double-Blind

**Key eligibility criteria**
- HCV genotype 1
- Treatment non-responder (relapse, partial or null response)
- No cirrhosis
- No HIV or HBV

Paritaprevir/ RTV (150/100 mg) co-formulated with Ombitasvir (25 mg) and administered once-daily. Dasabuvir (250 mg) + RBV (weight-based dosing) administered twice-daily.

*After week 12, placebo patients received open-label Paritaprevir/ RTV Ombitasvir + Dasabuvir + RBV for 12 weeks.

Primary outcome: SVR12.

Zeuzem S, et al. NEJM 2014;370:1604-14
SAPPHIRE-II Results: ITT SVR12 Rates >95% in All Prior Peginterferon/Ribavirin Response Groups

<table>
<thead>
<tr>
<th>Prior Response Group</th>
<th>SVR12, % Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Relapse</td>
<td>82/86</td>
</tr>
<tr>
<td>Prior Partial Response</td>
<td>65/65</td>
</tr>
<tr>
<td>Prior Null Response</td>
<td>139/146</td>
</tr>
</tbody>
</table>

Paritaprevir/ RTV Ombitasvir + Dasabuvir + RBV in HCV Genotype 1 Cirrhosis (TURQUOISE-II):

Phase 3 Study

Key eligibility criteria
- HCV genotype 1
- Treatment-naive and treatment-experienced
- Compensated cirrhosis (Child-Pugh score <6)
- HCV RNA >10K IU/mL
- No HIV or HBV

Paritaprevir/ RTV (150/100 mg) co-formulated with Ombitasvir (25 mg) and administered once-daily.
Dasabuvir (250 mg) + RBV (weight-based dosing) administered twice-daily.
Primary outcome: SVR12.

Zeuzem S, et al. NEJM 2014;370:1604-14
TURQUOISE-II Results:
ITT SVR12 Rates of 92% to 96%

<table>
<thead>
<tr>
<th>Weeks</th>
<th>SVR12 % Patients</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>191/208</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td>24</td>
<td>165/172</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SVR 80% in 1a null Responders who Received 12 weeks of therapy

The current standard of care: Genotypes 2/3

- HCV genotype 2, regardless of eligibility for IFN therapy or treatment failure with PEG/RBV: Sofosbuvir (400 mg) and weight-based RBV (1000-1200 mg) for 12 weeks
  - cirrhotics may benefit from extension to 16 weeks
- HCV genotype 3, regardless of eligibility for IFN therapy or treatment failure with PEG/RBV: Sofosbuvir (400 mg) and weight-based RBV (1000-1200 mg) for 24 weeks
  - Alternative regimen: HCV genotype 2&3 PEG/RBV nonresponders: Sofosbuvir (400 mg) and weight-based RBV (1000-1200 mg) plus weekly PEG for 12 weeks in IFN eligible patients
FUSION: Sofosbuvir + RBV by Fibrosis Level in Treatment-experienced Genotype 2


VALENCE: Sofosbuvir + RBV for 24 weeks
Genotype 3 IFN naïve, ineligible or treatment failures

Interferon-Free, All Oral Regimens
Other/Special Populations

Paritaprevir/r, Ombitasvir, Dasabuvir with RBV for 24 weeks for Liver Transplant HCV Patients: Preliminary Efficacy Results

- No patient had breakthrough
- One patient had a relapse (post-treatment day 3)
  - At the time of relapse, this patient had R155K in NS3 protease, M28T+Q30R in NS5A, and G554S+G557R in NS5B, none of which were present at baseline

Summary: To be continued

- The next big advance is here: all oral therapies for genotype 1 that are FDA approved
- Sofosbuvir/ledipasvir: (no RBV)
  - 8-12 weeks for naïve
  - 24 weeks for non-responder cirrhotic patients
- Paritaprevir/Ombitasvir/dasabuvir±RBV (approval by end of 2014)
  - 12 weeks for naïve, cirrhotic patients (with RBV)
  - 24 weeks for Genotype 1a null responders
  - 12 weeks no RBV for 1b non-cirrhotics
  - Sofosbuvir/simeprevir also available, not licensed together yet
Summary: To be continued

- Genotype 2 has been largely solved (12-16 weeks)
- Genotype 3 treatment failure with cirrhosis is now the most problematic to treat

- Special populations are becoming not so special
  - HIV/HCV patients
  - Post OLT patients

- Access to therapies will be important

The new components of treatment in HCV infection

- NS3
- NS5b
- NS5a
- NNI
Hepatitis C Therapy has Paralleled Helicobacter pylori Therapy

Selected Long-Duration Regimens for Helicobacter pylori Therapy

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Duration</th>
<th>Eradication rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprozole (10 mg twice daily), plus amoxicillin, 1 g twice daily, plus clarithromycin (750 mg twice daily)</td>
<td>14 days</td>
<td>80 to 95</td>
</tr>
<tr>
<td>Lansoprazole (30 mg twice daily), plus amoxicillin, 1 g twice daily, plus clarithromycin, 500 mg twice daily</td>
<td>10 to 14 days</td>
<td>86</td>
</tr>
<tr>
<td>Bismuth subcitrate</td>
<td>425 mg four times daily, plus metronidazole (Flagyl), 250 mg four times daily, plus tetraccline, 500 mg four times daily, plus histamine H2 blocker</td>
<td>14 days (H2 blocker) alone for an additional 14 days taken once or twice daily</td>
</tr>
</tbody>
</table>

All Oral Therapy
Duration 8–24 weeks

Polymerase Inhibitor
Protease Inhibitor
±
NS5a
±
Non-nucleoside Inhibitor
±
ribavirin

All Oral Therapy, single tablet

ACG Postgraduate Course • October 18–19, 2014