Treatment of Hepatitis C in Patients with Renal Insufficiency

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Robert Gish, MD: Relevant Disclosures To HCV

- **Consulting Board**: Bristol-Myers Squibb, Gilead, Merck & Co., Janssen, Abbvie

- **Honoraria for Promotional Talks**: Bristol-Myers Squibb, Gilead Sciences, Merck & Co., AbbVie, Janssen
Treatment of Hepatitis C in Patients with Renal Insufficiency

- Background and Staging of Renal Disease
- Treatment with Interferon-Based Regimens
- Treatment with Direct-Acting Antiviral Agents
- Hepatitis C and Renal Transplantation
- Summary
TREATMENT OF HCV IN PATIENTS WITH RENAL INSUFFICIENCY

Background and Staging Renal Disease
Hepatitis C Treatment Issues Related to Renal Disease

- Hepatitis C may be associated with or cause renal disease

- Treatment of hepatitis C and renal disease
  1. Treatment in patients with chronic renal insufficiency
  2. Treatment to prevent HCV causing renal disease
  3. Treatment post renal transplant for renal function and graft survival
Epidemiology of HCV in Patients on Hemodialysis (HD)

• In US, estimated HCV prevalence of 8%
  - (approximately 400,000 persons on HD)

• HCV prevalence 5X greater in HD patients than in general US population

• Risk factors for HCV infection among hemodialysis patients:
  - Number of years on dialysis
  - Number of blood product transfusions
  - Injection drug use
  - History of organ transplantation

Impact of Hepatitis C Infection on Hemodialysis Patients:

- Increased overall risk of mortality
- Increased risk of cirrhosis
- Increased incidence of hepatocellular cancer

Hepatitis C and Renal Disease
Hepatitis C as a Cause of Renal Disease

- HCV infection in patients with advanced liver failure increases risk for renal disease
- Chronic HCV infection associated with increased risk for renal cell carcinoma
- Chronic HCV infection accelerated renal disease in HIV-infected patients

Hepatitis C and Renal Disease

HCV as a Cause of Renal Disease: Immune Complex Disorders

- HCV-associated immune complex disorders that cause renal disease
  - Mixed Cryoglobulinemia: RF as a screening test; reflex to qualitative or quantitative cryoglobulin (type II cryoglobulins)
  - Glomerulonephritis (Membranoproliferative [MPGN] is the most common)
  - Polyarteritis nodosa

- Uncommon HCV-associated immune complex disorders that cause renal disease
  - Focal segmental glomerular sclerosis
  - Proliferative glomerulonephritis
  - Membranous glomerulonephritis
  - Fibrillary and immunotactoid glomerulopathies

Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney Damage with Normal or ↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney Damage with Mild ↓ GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

Source: NKF KDOQI Clinical Practice Guidelines for Chronic Kidney Disease
Treatment of HCV in Patients with Renal Insufficiency

Experience with Interferon-Based Therapies
Interferon Monotherapy for HD Patients with Chronic HCV
Analysis of the Literature on Efficacy (SVR)

Analysis of 8 Studies Using INF-alfa 2b Monotherapy 3 million units 3x/week

Peginterferon + Ribavirin for HCV in Hemodialysis Patients
Meta-Analysis of the Literature on Efficacy

Summary Estimates for SVR Rates

Analysis of 11 Studies (287 patients) Using PEG alfa-2a/PEG alfa-2b + RBV

PEG-IFN +/- Low-dose RBV (200 mg/day) in HCV GT1 on Hemodialysis

HELPER-1 Trial: Study Regimens

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 103</td>
<td></td>
<td>SVR24 N = 94</td>
<td></td>
</tr>
<tr>
<td>Peginterferon alfa-2a + Ribavirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 102</td>
<td>Peginterferon alfa-2a</td>
<td>SVR24 N = 91</td>
<td></td>
</tr>
</tbody>
</table>

Drug Dosing
Peginterferon alfa-2a 135 µg 1x/week
Low-dose Ribavirin: 200 mg once daily

PEG-IFN +/- Low-dose RBV (200 mg/day) in HCV GT1 on Hemodialysis
HELPER-1 Trial: Results

Virologic Responses

Drug Dosing
Peginterferon alfa-2a: 135 µg once weekly
Ribavirin: 200 mg daily

Controversies with Ribavirin Use in Advanced Renal Disease

• Not recommended with eGFR < 50 ml/min/1.73 m² in:
  - Package inserts for Rebetol, Ribasphere
  - KDIGO 2008 guidelines
  - 2009 AASLD guidelines

• Permitted with eGFR < 50 ml/min/1.73 m² (with dose reduction) in:
  - Package insert for CoPegus
  - 2014 AASLD/IDSA/IAS-USA guidelines
Experience with Direct-Acting Antiviral Agents
Treatment of Hepatitis C in Patients with Renal Disease
Possible Options using Direct Acting Antiviral Agents

- Sofosbuvir plus Ribavirin
- Simeprevir plus Sofosbuvir
- Ombitasvir-Paritaprevir-Ritonavir plus Dasabuvir (genotype 1)
- Ledipasvir-Sofosbuvir (pangenotypic)
- Sofosbuvir plus Daclatasvir*

*Daclatasvir was not FDA approved in United States as of July 1, 2015
### Sofosbuvir Pharmacokinetics in HCV-Negative Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Patient Renal Impairment</th>
<th>Sofosbuvir AUC*</th>
<th>GS-3310007 AUC*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Following Single 400 mg dose of sofosbuvir</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR ≥50 and &lt; 80 mL/min/1.73 m²</td>
<td>†61%</td>
<td>†55%</td>
</tr>
<tr>
<td>eGFR ≥30 and &lt; 50 mL/min/1.73 m²</td>
<td>†107%</td>
<td>†88%</td>
</tr>
<tr>
<td>eGFR &lt;30 mL/min/1.73 m²</td>
<td>†171%</td>
<td>†451%</td>
</tr>
<tr>
<td>ESRD requiring hemodialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosed 1 hour before hemodialysis</td>
<td>†28%</td>
<td>†1280%</td>
</tr>
<tr>
<td>Dosed 1 hour after hemodialysis</td>
<td>†60%</td>
<td>†2070%</td>
</tr>
</tbody>
</table>

*AUC given relative to subjects with normal renal function

**Source:** Sofosbuvir Prescribing Information, Gilead Sciences.
Simeprevir Pharmacokinetics
Severe Renal Impairment versus Healthy Subjects

Linear Mean Plasma Concentration-Time Profiles

Bars represent standard deviation

Source: Janssen Products
HCV-Target and Patients with Renal Disease: Features

- **Design**: Longitudinal, cohort study with sofosbuvir-containing regimens, including patients with renal disease

- **Setting**: 56 centers in US, Germany, and Canada

- **Entry Criteria**
  - Chronic HCV treated with sofosbuvir-containing regimen
  - HCV genotype 1-6
  - Age 18 or older
  - Treatment naïve and treatment experienced
  - Includes patients with baseline renal insufficiency
  - Includes patients with cirrhosis

- **Primary End-Points**
  - Efficacy (SVR12), safety
Sofosbuvir-Containing Regimens in Patients with Renal Disease HCV -TARGET

HCV TARGET: SVR12, by Baseline eGFR

Source: Saxena V, et al. 50th EASL. 2015; Abstract LP08.
Sofosbuvir-Containing Regimens including Patients with Renal Disease

HCV-TARGET Trial: Result

HCV-TARGET Trial: SVR12 Results by Baseline eGFR and Regimen

Abbreviations: SOF = sofosbuvir; PEG = peginterferon; RBV = ribavirin; SMV = simeprevir

Source: Saxena V, et al. 50th EASL. 2015; Abstract LP08.
# RUBY-I: Study Design

## RUBY-I: Features

- **Design**: Phase 3b, randomized, open-label trial evaluating safety and efficacy of 3D (ombitasvir-paritaprevir-ritonavir and dasabuvir) with or without ribavirin for 12 weeks in treatment-naïve patients with chronic HCV GT1 and advanced kidney disease.

- **Setting**: 9 sites in United States.

- **Entry Criteria**
  - Adults with chronic HCV genotype 1 infection
  - Chronic kidney disease stage 4 or 5 (eGFR <30 mL/min/1.73 m²) +/- HD
  - Plasma HCV RNA greater than 1,000 IU/mL
  - Absence of cirrhosis
  - Absence of coinfection with HBV or HIV
  - Baseline Hb ≥10 g/dL

- **Primary End-Point**: SVR12

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# Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 & Renal Disease

**RUBY-I: Regimens**

<table>
<thead>
<tr>
<th>Week</th>
<th>Drug Dosing</th>
<th>GT 1a n = 13</th>
<th>GT 1b n = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily</td>
<td>Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir + Ribavirin</td>
<td>Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Ribavirin for patients not on hemodialysis: 200 mg once daily</td>
<td>SVR12</td>
<td>SVR12</td>
</tr>
</tbody>
</table>

**Drug Dosing**
- Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily
- Ribavirin for patients not on hemodialysis: 200 mg once daily
- Ribavirin for patients on hemodialysis: 200 mg given 4 hours before each hemodialysis session

*Source: Pockros PJ, et al. 50th EASL. 2015; Abstract L01.*
Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 & Renal Disease
RUBY-I: Baseline Results

RUBY-I: SVR 12 Rates*

<table>
<thead>
<tr>
<th></th>
<th>GT1a: 3D + RBV</th>
<th>GT1b: 3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOT</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>SVR4</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>SVR12</td>
<td>100</td>
<td>0/0</td>
</tr>
</tbody>
</table>

3D = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; RBV = ribavirin; EOT = end of treatment

AASLD/IDSA/IAS-USA 2015 HCV Treatment Recommendations

### Recommendations for Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Dosage adjustments for patients with mild to moderate renal impairment (CrCl 30 mL/min-80 mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir: no dosage adjustment required</td>
</tr>
<tr>
<td>Simeprevir: no dosage adjustment required</td>
</tr>
<tr>
<td>Ledipasvir-sofosbuvir: no dosage adjustment required</td>
</tr>
<tr>
<td>Ombitasvir-paritaprevir-ritonavir + dasabuvir: no dosage adjustment required</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosage adjustments for patients with severe renal impairment (CrCl &lt;30 mL/min or ESRD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment can be contemplated after consultation with an expert, because safety and efficacy data are not available for these patients.</td>
</tr>
</tbody>
</table>

*Recommendations for patients with renal impairment, including severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease requiring hemodialysis or peritoneal dialysis*
TREATMENT OF HCV IN PATIENTS WITH RENAL INSUFFICIENCY

HCV and Renal Transplantation
Impact of HCV on Outcome of Renal Transplantation

- HCV increases glomerulonephritis in transplanted kidney
- HCV reduces renal allograft survival
- HCV decreases long-term patient survival

- HCV infection is not a contraindication to renal transplantation unless portal hypertension is present or there is decompensated liver disease since patient survival with RT is better than with dialysis

Relative Risk of Death among Patients Undergoing Renal Transplantation versus those who Remained on Dialysis

Relative Risk of Death (all causes): Transplanted versus Dialysis

Hepatitis C and Renal Disease
Rationale for HCV Treatment in Renal Transplant Candidate

- Eradicate HCV as immunologic stimulus to B-cells to decrease immune complex formation and impact vasculitis or glomerulonephritis
- Decrease extrahepatic HCV-related complications
- Prevent HCV-related post-transplant complications
  - Interaction with HCV immune complexes and calcineurin inhibitor related renal toxicity
- HCV-related liver disease may accelerate with post-transplant immunosuppression
- Post-transplant treatment extremely difficult due to risk of graft rejection from interferon (historical)
Treatment of HCV after Renal Transplantation

• Interferon-based therapy relatively contraindicated because of risk of allograft rejection and loss

• Post-transplant interferon/ribavirin recommended only for
  - Fibrosing cholestatic hepatitis
    ◦ IF daclatasvir compassionate use not available
  - Life-threatening vasculitis

• Interferon-free regimens will provide new options
Treatment of HCV Post-Renal Transplant

• Renal function less problematic depending on:
  - Use, dose, & blood levels of calcineurin inhibitor (cyclosporine, tacrolimus)
  - Improvement in GFR with graft recovery
  - History of rejection and residual renal damage

• Address drug-drug interactions per medication & drug class

• Higher HCV RNA levels due to immunosuppression may impact SVR rates

• No effective therapy yet published in controlled trials
TREATMENT OF HCV IN PATIENTS WITH RENAL INSUFFICIENCY

Summary and Recommendations
Treatment of Hepatitis C in Patients with Renal Insufficiency

Summary Points

• Renal disease severity should guide treatment decisions
• Interferon- and Peginterferon-based Rx of historical importance only
• Maximize EPO use when using ribavirin in this patient population
• First-generation HCV protease inhibitors not recommended
• No dose adjustments with DAAs if GFR ≥ 30 mL/min
• Limited data with DAAs in patients with GFR <30 mL/min
• Obtain expert consultation if GFR <30 mL/min, especially HD patients
• Renal transplant candidates should receive HCV treatment with DAAs
  - Either before or after transplantation, depending on clinical scenario