Treatment of Hepatitis C and Renal Disease

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HCV and Renal Disease

- HCV infection may lead to renal disease or be associated with renal disease
  - Mixed cryoglobulinemia (type II cryoglobulins, or + RF)\(^1\)
  - Membranoproliferative glomerulonephritis (MPGN)\(^1\)
  - Polyarteritis nodosa\(^2\)
- Less clearly related to HCV\(^1\)
  - Focal segmental glomerulosclerosis
  - Proliferative glomerulonephritis
  - Membranous glomerulonephritis
  - Fibrillary and immunotactoid glomerulopathies
- Diabetes (direct link to HCV) and hypertension common in HCV infection\(^3\)


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

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>

Dose Adjustments for Renal Impairment

- No reduction required for any of the following medications with GFR >30
  - Sofosbuvir, Velpatasvir, Ledipasvir, Daclatasvir, Ombitasvir, Dasabuvir, Paritaprevir, Simeprevir, Elbasvir, Grazeprevir
- For GFR <50, dose reduction is required for:
  - PEG-IFN
  - Ribavirin

Dose Adjustments for Renal Impairment

- For GFR <30 and >15, and for patients on hemodialysis
  - Dose reduction of RBV to 200 mg/day
  - No dose reduction for grazeprevir/elbasvir
  - Limited data for Paritaprevir, ombitasvir, dasabuvir, daclatasvir
  - Minimal data for ledipasvir, simeprevir, velapatasvir


Current Treatment of Hepatitis C in Patients whose CrCl >30

- No dose adjustment with:
  - Daclatasvir
  - FDC Ledipasvir/sofosbuvir
  - FDC Sofosbuvir/velpatasvir
  - FDC Paritaprevir/ritonavir/ombitasvir + dasabuvir
  - Simeprevir/sofosbuvir
  - Grazeprevir/elbasvir
Current Treatment of Hepatitis C in Patients whose CrCl <30

- Elbasvir/grazeprevir
  - GT 1a 12 weeks with RBV
  - GT 1a with RAV 16 weeks with RBV
  - GT 1b 12 weeks without RBV
- FDC Paritaprevir/ritonavir/ombitasvir + dasabuvir
  - GT 1a 12 weeks with RBV
  - GT 1b 12 weeks without RBV

WHY NOT SOFOSBUVIR BASED REGIMENS FOR RENAL DISEASE?
Metabolism of Sofosbuvir

Sofosbuvir Pharmacokinetics
HCV-Negative Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Patient Renal Impairment</th>
<th>Sofosbuvir AUC*</th>
<th>GS-331007 AUC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Following Single 400 mg dose of sofosbuvir</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

Sofosbuvir Prescribing Information, Gilead Sciences May 2015
Sofosbuvir

• No dose recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m²) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite

• Similar rapid virologic decline observed to those with normal renal function
• SVR12: 40%

• SOF 200 mg + RBV was safe and relatively well tolerated in pts with severe renal impairment with exacerbation of anemia via RBV-induced hemolysis as primary AE

• Mean eGFR change from baseline to EOT (Wk 24): -3.12 mL/min
• No treatment-emergent clinically significant ECG results


SOF + RBV in Pts With Severe Renal Impairment

• Similar rapid virologic decline observed to those with normal renal function
• SVR12: 40%

• Comparing SOF and GS-331007 exposures compared with historical HCV-infected population
• SOF 200 mg + RBV was safe and relatively well tolerated in pts with severe renal impairment with exacerbation of anemia via RBV-induced hemolysis as primary AE

HCV AND HEMODIALYSIS

Epidemiology of HCV in Patients on Hemodialysis

- In U.S., estimated HCV prevalence of 8%
  - (approximately 400,000 persons on HD)
- HCV prevalence 5X greater in HD patients than in general U.S. 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


DATA ON HCV AND RENAL DISEASE:
THE PAST
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

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

### HELPER-1 Trial: Study Regimens

#### Virologic Responses

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

#### Drug Dosing

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


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### HELPER-1 Trial: Results

#### Virologic Responses

<table>
<thead>
<tr>
<th>Virologic Response (%)</th>
<th>Peginterferon + Ribavirin</th>
<th>Peginterferon</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVR</td>
<td>51/103</td>
<td>36/102</td>
</tr>
<tr>
<td>ETVR</td>
<td>87/101</td>
<td>84/102</td>
</tr>
<tr>
<td>SVR24</td>
<td>64/103</td>
<td>33/102</td>
</tr>
</tbody>
</table>

#### Drug Dosing

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

CURRENT DATA ON HCV AND RENAL DISEASE

Sofosbuvir-Containing Regimens including Patients with Renal Disease
HCV-TARGET Trial: Result

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

<table>
<thead>
<tr>
<th>Estimated GFR mL/min/1.73 m²</th>
<th>Patients with SVR 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30</td>
<td>100 100 100 100 93 81 80 80 91 79</td>
</tr>
<tr>
<td>30-45</td>
<td>1/1 2/2 1/3 2/2 9/9 20/25 13/14 8/15 22/29 38/45</td>
</tr>
<tr>
<td>46-60</td>
<td>1/6 3/17 2/20 3/21 3/29 2/12 2/13 2/32</td>
</tr>
<tr>
<td>&gt;60</td>
<td>88/88 87/71 71/71 80/60 52/52 111/37</td>
</tr>
</tbody>
</table>

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

Saxena V, et al. 50th EASL, 2015; Abstract LP08.
HCV TARGET: Safety Outcomes With SOF Regimens by Baseline eGFR

<table>
<thead>
<tr>
<th>Safety Outcome in Pts Who Completed SOF-Containing Therapy, n (%)</th>
<th>eGFR ≤ 30 (n = 17)</th>
<th>eGFR 31-45 (n = 56)</th>
<th>eGFR 46-60 (n = 157)</th>
<th>eGFR &gt; 60 (n = 1559)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia AEs</td>
<td>6 (35)</td>
<td>16 (29)</td>
<td>37 (24)</td>
<td>246 (16)</td>
</tr>
<tr>
<td>Transfusions</td>
<td>2 (12)</td>
<td>5 (9)</td>
<td>3 (2)</td>
<td>31 (2)</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>1 (6)</td>
<td>8 (14)</td>
<td>14 (9)</td>
<td>50 (3)</td>
</tr>
<tr>
<td>Reduction in RBV dose</td>
<td>3 (18)</td>
<td>8 (30)</td>
<td>33 (42)</td>
<td>185 (19)</td>
</tr>
<tr>
<td>RBV discontinuation</td>
<td>0</td>
<td>4 (15)</td>
<td>1 (1)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>5 (29)</td>
<td>6 (11)</td>
<td>4 (3)</td>
<td>14 (1)</td>
</tr>
<tr>
<td>Renal or urinary system AEs</td>
<td>5 (29)</td>
<td>6 (11)</td>
<td>13 (8)</td>
<td>84 (5)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>3 (18)</td>
<td>13 (23)</td>
<td>8 (5)</td>
<td>100 (6)</td>
</tr>
<tr>
<td>Cardiac AEs</td>
<td>1 (6)</td>
<td>2 (4)</td>
<td>8 (5)</td>
<td>53 (3)</td>
</tr>
</tbody>
</table>


CLINICAL STUDIES IN ADVANCED RENAL DISEASE
C-SURFER: Grazoprevir/Elbasvir in Pts With GT1 HCV and Stage 4 or 5 CKD

- NO RBV IN THIS STUDY*

<table>
<thead>
<tr>
<th>GT1 HCV-infected pts with stage 4/5 CKD (n = 224)</th>
<th>Treatment Wk 12</th>
<th>Follow-up Wk 4</th>
<th>Follow-up Wk 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grazoprevir/Elbasvir (n = 111)</td>
<td><strong>Randomized period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 113)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grazoprevir/Elbasvir (n = 113)</td>
<td><strong>Open-label period</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Grazoprevir/elbasvir dosed orally 100 mg/50 mg once daily.


C-SURFER: KEY INCLUSION/EXCLUSION CRITERIA

- HCV GT1 infection
- Treatment-naive and treatment-experienced patients
- CKD stage 4/5 (± hemodialysis dependence)
- Compensated cirrhosis allowed
- HBV and HIV negative
C-SURFER: DEMOGRAPHICS

<table>
<thead>
<tr>
<th></th>
<th>GZR + EBR (ITG + PK group)</th>
<th>Placebo (DTG)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 weeks (n = 122)</td>
<td>12 weeks (n = 113)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>92 (75)</td>
<td>80 (71)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (25)</td>
<td>33 (29)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>61 (50)</td>
<td>48 (43)</td>
</tr>
<tr>
<td>African-American</td>
<td>55 (45)</td>
<td>53 (47)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (4)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (&lt;1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td><strong>HCV genotype, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1a</td>
<td>63 (52)</td>
<td>59 (52)</td>
</tr>
<tr>
<td>G1b</td>
<td>58 (48)</td>
<td>53 (47)</td>
</tr>
<tr>
<td>G1 other</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td><strong>Prior treatment history, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive</td>
<td>101 (83)</td>
<td>88 (78)</td>
</tr>
<tr>
<td>Experienced</td>
<td>21 (17)</td>
<td>25 (22)</td>
</tr>
<tr>
<td><strong>Cirrhosis, n (%)</strong></td>
<td>7 (6)</td>
<td>7 (6)</td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>44 (36)</td>
<td>36 (32)</td>
</tr>
<tr>
<td><strong>Dialysis, n (%)</strong></td>
<td>92 (75)</td>
<td>87 (77)</td>
</tr>
<tr>
<td><strong>CKD stage, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stage 4</td>
<td>22 (18)</td>
<td>22 (19)</td>
</tr>
<tr>
<td>stage 5</td>
<td>100 (82)</td>
<td>91 (81)</td>
</tr>
</tbody>
</table>

DTG = deferred treatment group; ITG = immediate treatment group; PK = Intensive PK group

C-SURFER: SVR12: IMMEDIATE TREATMENT GROUP (ITG)

**Modified Full Analysis Set**

- Relapse: 1*
- Discontinued unrelated to Tx: 0

**Full Analysis Set**

- Relapse: 1
- Discontinued unrelated to Tx: 6†

MFAS = primary efficacy analysis; FAS was a secondary analysis
*Noncirrhotic, interferon-intolerant patient with HCV GT1b infection relapsed at FW12
†Lost to follow-up (n=2), n=1 each for death, non-compliance, withdrawal by subject, and withdrawal by physician (due to violent behavior)
C-surfer virologic response (ITG)

<table>
<thead>
<tr>
<th></th>
<th>TW2 (%)</th>
<th>TW4 (%)</th>
<th>TW12 (EOT) (%)</th>
<th>FUW4 (%)</th>
<th>FUW12 (SVR12) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>66%</td>
<td>90%</td>
<td>100%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td>81/122</td>
<td>109/121</td>
<td>119/119</td>
<td>118/118</td>
<td>115/116</td>
</tr>
</tbody>
</table>

1 non-cirrhotic patient with HCV GT1b infection relapsed at FUW12

*Efficacy is presented for the modified full analysis set population (mFAS)
Roth et al. Lancet 2015

C-SURFER: Efficacy and Safety Results

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Grazoprevir/Elbasvir (Randomized Tx) (n = 111)</th>
<th>Placebo (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AEs</td>
<td>14.4</td>
<td>16.8</td>
</tr>
<tr>
<td>D/c due to AE</td>
<td>0</td>
<td>4.4</td>
</tr>
<tr>
<td>Death</td>
<td>0.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Hb decr from BL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1 grade</td>
<td>24.3</td>
<td>26.5</td>
</tr>
<tr>
<td>• 2 grades</td>
<td>12.6</td>
<td>7.1</td>
</tr>
<tr>
<td>• 3 grades</td>
<td>3.6</td>
<td>1.8</td>
</tr>
<tr>
<td>• 4 grades</td>
<td>0</td>
<td>0.9</td>
</tr>
</tbody>
</table>

GZR/EBV for 12 wks

ELBASVIR / GRAZEPREVIR GT 1 FDA APPROVAL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1a TN or PEG/RBV TE without baseline RAV's</td>
<td>Elbasvir/grazeprevir 12 weeks</td>
</tr>
<tr>
<td>GT 1a TN or PEG/RBV TE with baseline RAV's</td>
<td>Elbasvir/grazeprevir + RBV 16 weeks</td>
</tr>
<tr>
<td>GT 1b TN or PEG/RBV TE</td>
<td>Elbasvir/grazeprevir 12 weeks</td>
</tr>
<tr>
<td>GT 1a/1b PEG/RBV/PI TE</td>
<td>Elbasvir/grazeprevir 12 weeks</td>
</tr>
</tbody>
</table>

**Despite C-Surfer study without RBV, the FDA has approved treatment for renal disease with RBV although no CKD patients were treated with RBV**

Zepatier PI Merck January 28, 2016

Ruby-1 Study

- **3D**: Co-formulated OBV/PTV/r (25/150/100 mg QD) and DSV (250 mg BID)
- **For GT1a**: RBV 200 mg QD
- **For GT1b**: No RBV

Ruby 1: Ombitasvir/Paritaprevir/r + Dasabuvir + RBV in G1 with stage 4/5 kidney disease

- 12 week treatment
- Non-cirrhotics
- 14 on dialysis
- 13 G1a, 7 G1b
- 1 subject relapsed
  - 49 yo AA, F3, IL28 B CT, BMI 37
  - < 92% medication adherence
- 1 subject died 14 days after treatment from heart disease

Pockros et al. Gastro 2016

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

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GT 1a</strong>&lt;br&gt;n = 13</td>
<td><strong>Ombitasvir-Paritaprevir-Ritonavir</strong> and Dasabuvir + Ribavirin</td>
<td></td>
<td>SVR12</td>
</tr>
<tr>
<td><strong>GT 1b</strong>&lt;br&gt;n = 7</td>
<td><strong>Ombitasvir-Paritaprevir-Ritonavir</strong> and Dasabuvir</td>
<td></td>
<td>GVR12</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

ACG 2016 Southern Hepatitis School
Copyright 2016 American College of Gastroenterology
Ruby 1 Results

Expedition-IV: Glecaprevir/Pibrentasvir in renal impairment in genotype 1-6

- 104 subjects with CKD
  - 82% on dialysis
  - 87% CKD stage 5
  - 13% CKD stage 4
- Genotype breakdown
  - 153%
  - 2 16%
  - 3 11%
  - 4 19%
  - 5 1%
  - 6 1%
- SVR 4 99% (103/104)
- 4 adverse events leading to discontinuation

Gane et al. AASLD 2016 Abstract LB-11
HCV TREATMENT AND KIDNEY TRANSPLANTATION

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 contraindicated because of risk of allograft rejection and loss
- Interferon-free regimens provide new options

To treat or not treat patients waiting for kidney transplantation

**FOR**
- Eradicate HCV
- Effective therapies

**AGAINST**
- Potentially prolong wait for kidney
  - HCV + kidneys
CONCLUSIONS

Recommended regimen for patients with CrCl below 30 ml/min but for whom the urgency to treat is high and renal transplant is not an immediate option

• Genotype 1a
  – Elbasvir/grazeprevir for 12 weeks without RAV
  – Elbasvir/grazeprevir for 16 weeks with RAV
  – Paritaprevir/ritonavir/ombitasvir with twice a day dasabuvir with RBV for 12 weeks

• Genotype 1b
  – Elbasvir/grazeprevir for 12 weeks
  – Paritaprevir/ritonavir/ombitasvir with dasabuvir

• Genotype 4
  – Elbasvir/grazeprevir for 12 weeks
Recommended regimen for patients with CrCl below 30 ml/min or ESRD for whom the urgency to treat is high and renal transplant is not an immediate option

- Genotype 2, 3, 5*, or 6*
  - PEG-IFN and dose adjusted RBV at 200 mg daily

- Several small studies show safety of SOF/LDV in HD