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 medication with GFR >50
  - Sofosbuvir, Ledipasvir, Daclatasvir, Ombitasvir, Dasabuvir, Paritaprevir, Simeprevir, Elbasvir, Grazoprevir
- For GFR >30 and less than 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

Current Treatment of Hepatitis C in Patients whose CrCl >30

• No dose adjustment with:
  – Daclatasvir
  – FDC Ledipasvir/sofosbuvir
  – FDC Paritaprevir/ritonavir/ombitasvir + dasabuvir
  – Simeprevir/sofosbuvir
  – Grazeprevir/elbasvir
Metabolism of Sofosbuvir

SOFOSBUVIR
GS-588500
GS-60965
GS-461203
GS-331007
INACTIVE METABOLITE
RENALLY EXCRETED
Cat-A, CES1
Hint-1
Kinase

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 and GS-331007 Pharmacokinetics

- Comparable SOF and ~4-fold higher 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
- Mean eGFR change from baseline to EOT (Wk 24): -3.12 mL/min
- No treatment-emergent clinically significant ECG results

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

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

<table>
<thead>
<tr>
<th>Summary Estimates for SVR Rates</th>
<th>All Studies</th>
<th>Cohort Studies</th>
<th>Controlled Studies</th>
<th>Peg-IFN alfa-2a</th>
<th>Peg-IFN alfa-2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a</td>
<td>60%</td>
<td>54%</td>
<td>86%</td>
<td>57%</td>
<td>63%</td>
</tr>
</tbody>
</table>


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>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

Current data on HCV and renal disease.
Efficacy and Safety of Ombitasvir/Paritaprevir/r + Dasabuvir ± Ribavirin According to Baseline Renal Function: Analysis of 2005 patients enrolled in Six Phase 3 Trials

Sulkowski et al. HepDart 2015

TARGET: SVR12 With SOF Regimens by Baseline eGFR and Cirrhosis Status

- Sofosbuvir + simeprevir most common regimen used
- Overall SVR12 rates high and similar (>80%) across renal function strata in pts with known treatment outcome

## Sofosbuvir-Containing Regimens including Patients with Renal Disease

### HCV-TARGET Trial: Result

#### 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</td>
</tr>
<tr>
<td>30-45</td>
<td>80/80</td>
</tr>
<tr>
<td>46-60</td>
<td>80/80</td>
</tr>
<tr>
<td>&gt;60</td>
<td>84/87</td>
</tr>
</tbody>
</table>

**Note:**
- 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>

**Note:**
CLINICAL STUDIES IN ADVANCED RENAL DISEASE

C-SURFER: Grazoprevir/Elbasvir in Pts With GT1 HCV and Stage 4 or 5 CKD

Grazoprevir/Elbasvir (n = 111)  
Placebo (n = 113)

GT1 HCV-infected pts with stage 4/5 CKD (n = 224)

Treatment Wk 12  
Follow-up Wk 4  
Follow-up Wk 16

Open-label period  

Grazoprevir/Elbasvir (n = 113)


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)
  - CKD stage 4: eGFR 15-29 mL/min/1.73m²
  - CKD stage 5: eGFR <15 mL/min/1.73m² or on dialysis.
  - target 20% non-hemodialysis patients
- Compensated cirrhosis allowed
  - Liver staging was based on biopsy within 24 months of enrolment; transient elastography (Fibroscan) within 12 months of enrolment; or a combination of Fibrotest score of >0.75 and an AST:platelet ratio index of >2
  - Patients with presence or history of ascites, gastric or variceal bleeding, hepatic encephalopathy, or other signs/symptoms of advanced liver disease were excluded
- HBV and HIV negative

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate

C-SURFER: DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Gender, n (%)</th>
<th>GZR + EBR (ITG + PK group) 12 weeks (n = 122)</th>
<th>Placebo (DTG) 12 weeks (n = 113)</th>
</tr>
</thead>
<tbody>
<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>Race, n (%)</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>HCV genotype, n (%)</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>Prior treatment history, n (%)</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>Cirrhosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (6)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44 (36)</td>
<td>36 (32)</td>
</tr>
<tr>
<td>Dialysis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>92 (75)</td>
<td>87 (77)</td>
</tr>
<tr>
<td>CKD stage, n (%)</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 | Full Analysis Set
---|---
Relapse | 1* | 1
Discontinued unrelated to Tx | 0 | 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)

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

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

SVR12 (%)

- Full Set: 94/100/100/98.2/98.9/97.6
- Cirrhosis: 94/100/100/98.2/98.9/97.6
- GT1a HCV: 94/100/100/98.2/98.9/97.6
- GT1b HCV: 94/100/100/98.2/98.9/97.6
- On HD: 94/100/100/98.2/98.9/97.6
- Diabetic: 94/100/100/98.2/98.9/97.6

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>

Zepatier PI Merck January 28, 2016
**Ruby-1 Study**

- **Open-label Treatment**
  - GT1b: Paritaprevir/r/Ombitasvir + dasabuvir
  - GT1a: Paritaprevir/r/Ombitasvir + dasabuvir + RBV

- **SVR4**
- **SVR12**

- **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


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

- 12 week treatment
- Non-cirrhotics
- 14 on dialysis
- 13 G 1a, 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 AASLD 2015 Abstract 1039
HCV TREATMENT AND KIDNEY 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

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

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


<table>
<thead>
<tr>
<th>Time Period</th>
<th>Relative Risk of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 3 months</td>
<td>4.75</td>
</tr>
<tr>
<td>3 to 6 months</td>
<td>1.76</td>
</tr>
<tr>
<td>7 months to 4 years</td>
<td>0.31</td>
</tr>
<tr>
<td>Longer than 4 years</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Above red line = higher death risk with Renal Transplant
Below red line = higher death risk with Dialysis

To treat or not treat patients waiting for kidney transplantation

**FOR**
- Eradicate HCV
- Effective therapies

**AGAINST**
- Potentially prolong wait for kidney
- No approved therapies
CONCLUSIONS

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

- Genotype 1a
  - Elbasvir/grazeprevir for 12 weeks

- Genotype 1b
  - Elbasvir/grazeprevir for 12 weeks
  - Paritaprevir/ritonavir/ombitasvir with twice a day 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

- Genotype 4
  - Elbasvir/grazeprevir for 12 weeks


<table>
<thead>
<tr>
<th>eGFR/CrCl</th>
<th>OMV/PTV/RTV + DSV</th>
<th>LDV/SOF</th>
<th>SMV + SOF</th>
<th>DCV + SOF</th>
<th>RBV</th>
<th>ELB/GRZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-50 mL/min</td>
<td>No adjustment needed</td>
<td>No adjustment needed</td>
<td>No adjustment needed</td>
<td>Alternating 200 mg and 400 mg every other day</td>
<td>No adjustment needed</td>
<td></td>
</tr>
<tr>
<td>15-30 mL/min</td>
<td>Safety and efficacy not established</td>
<td>Safety and efficacy not established</td>
<td>No adjustment needed for SMV or DCV; Safety and efficacy of SOF not established</td>
<td>200 mg/day</td>
<td>No adjustment needed</td>
<td></td>
</tr>
<tr>
<td>&lt;15 mL/min or hemodialysis</td>
<td>Safety and efficacy not established</td>
<td>Safety and efficacy not established</td>
<td>Safety and efficacy not established</td>
<td>200 mg/day</td>
<td>No adjustment needed</td>
<td></td>
</tr>
</tbody>
</table>