Treatment of Hepatitis C and Renal Disease

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Not caused by HCV
- Congenital
- Diabetes
- Drugs
- Hypertension
- Intrinsic renal disease

Secondary to HCV
- Cryoglobulinemia
- MPGN
- PAN
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 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 Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>eGFR/CrCl (mL/min)</th>
<th>PEG-IFN</th>
<th>RBV</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Daclatasvir</th>
<th>Ombitasvir</th>
<th>Dasabuvir</th>
<th>Paritaprevir</th>
<th>Simeprevir</th>
</tr>
</thead>
</table>

Dose Adjustments for Patients with Severe Renal Impairment CrCl < 30

<table>
<thead>
<tr>
<th>PEG-IFN</th>
<th>RBV</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Daclatasvir</th>
<th>Ombitasvir</th>
<th>Dasabuvir</th>
<th>Paritaprevir</th>
<th>Simeprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% reduction</td>
<td>200 mg/d</td>
<td>LDA</td>
<td>No data</td>
<td>LDA</td>
<td>LDA</td>
<td>LDA</td>
<td>LDA</td>
<td>Standard</td>
</tr>
</tbody>
</table>

Dose Adjustments for Patients on Hemodialysis

<table>
<thead>
<tr>
<th>PEG-IFN</th>
<th>RBV</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Daclatasvir</th>
<th>Ombitasvir</th>
<th>Dasabuvir</th>
<th>Paritaprevir</th>
<th>Simeprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% reduction</td>
<td>200 mg/d</td>
<td>LDA</td>
<td>No data</td>
<td>LDA</td>
<td>LDA</td>
<td>LDA</td>
<td>LDA</td>
<td>LDA</td>
</tr>
</tbody>
</table>

LDA = limited data available


Current Treatment of Hepatitis C in Patients whose CrCl > 30 and <50

- No dose adjustment with:
  - Daclatasvir
  - FDC Ledipasvir/sofosbuvir
  - FDC Paritaprevir/ritonavir/ombitasvir + dasabuvir
  - Simeprevir/sofosbuvir
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) <30mL/min/1.73m²) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.

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

CURRENT DATA ON HCV AND RENAL DISEASE

Sofosbuvir-Containing Regimens including Patients with Renal Disease

HCV-TARGET Trial: Result

Saxena V, et al. 50th EASL, 2015; Abstract LP08.

Abbreviations: SOF = sofosbuvir; PEG = peginterferon; RBV = ribavirin; SMV = simeprevir
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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Transfusions</td>
<td>6 (35)</td>
<td>16 (29)</td>
<td>37 (24)</td>
<td>246 (16)</td>
</tr>
<tr>
<td>• Erythropoietin</td>
<td>2 (12)</td>
<td>5 (9)</td>
<td>3 (2)</td>
<td>31 (2)</td>
</tr>
<tr>
<td>• Reduction in RBV dose</td>
<td>1 (6)</td>
<td>8 (14)</td>
<td>14 (9)</td>
<td>50 (3)</td>
</tr>
<tr>
<td>• RBV discontinuation</td>
<td>3 (38)</td>
<td>8 (30)</td>
<td>33 (42)</td>
<td>185 (19)</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal or urinary system AEs</td>
<td>5 (29)</td>
<td>6 (11)</td>
<td>4 (3)</td>
<td>14 (1)</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

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

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

Randomized period
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; 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></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><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>95 (81)</td>
</tr>
</tbody>
</table>

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

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### C-surfer virologic response (ITG)

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

ACG Hepatitis School
December 5, 2015 - Nashville, Tennessee

ACG 2015 Nashville Hepatitis School
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C-SURFER: Efficacy and Safety Results


Ruby-1 Study:

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 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.


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

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 30ml/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
  – Paritaprevir/ritonavir/ombitasvir with twice daily dasabuvir plus RBV at reduced doses (200 mg three times a week to daily)
    • RBV should be restricted to patients with HgB > 10 g/dL

• Genotype 1b
  – Paritaprevir/ritonavir/ombitasvir with twice dasabuvir

• Genotype 4
  – Paritaprevir/ritonavir/ombitasvir
Recommended regimen for patients with CrCl below 30ml/min who do not have cirrhosis but for whom the urgency to treat is high and renal transplant is not an immediate option, who are RBV intolerant or ineligible

- Consultation with an expert is recommended, to assess the appropriateness of a sofosbuvir-containing regimen, because safety and efficacy is not available in this setting.


AASLD/IDSA Dosing Considerations in With Renal Impairment

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></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></td>
</tr>
<tr>
<td>15-30 mL/min</td>
<td>No adjustment needed</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></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></td>
</tr>
</tbody>
</table>

In noncirrhotic pts for whom tx is urgent and renal transplant not an immediate option:
- Recommended if RBV intolerant/ ineligible, in consultation with expert[3]