HCV Infection in the CKD and ESRD Patient: Who to Treat and When

David Roth, MD
William W. Anderson Professor of Nephrology
University of Miami Miller School of Medicine
Miami, Florida

Disclosures

- Scientific Advisory Board: Merck; Abbvie; Bristol-Myers Squibb.
- Consultant: Merck and Co.

Objectives

- Review the clinical impact of HCV infection in patients with CKD and ESRD.
- Identify what effect HCV antiviral treatment has on outcomes in CKD and ESRD patients.
- Review the safety and efficacy of the second generation direct acting antiviral agents in patients with kidney disease.
- Discuss the management of the HCV-infected kidney transplant candidate, the treatment of viremic kidney transplant recipients and the use of kidneys from HCV-positive organ donors.
Case Presentation

- 61 y/o AA male with a history of T2D for 20 yrs and HTN first seen 5 years ago with CKD3 (eGFR 45ml/min).
- Initial work-up: US with increased echogenicity but otherwise normal appearing kidneys, 2.5 gms of protein/24hr, U/A with protein and 2-5 RBC/hpf with all serology, HBV, HIV, SPEP, and FLC negative except for HCV ELISA positive.
- The patient was lost to follow-up and presented recently with edema and poorly controlled HTN and an eGFR of 14 ml/min.

Case Presentation: Questions

1. What other testing to evaluate the positive HCV ELISA should have been done at initial presentation? Would antiviral treatment have been appropriate at that time?
2. If presenting today as he did 5 years ago, should this patient be treated with antiviral agents to eradicate his HCV infection?
3. Should the patient be referred for kidney transplantation, sent to see a hepatologist, both or neither at this time?
4. Should treatment for HCV be started now? Would post transplant DAA treatment be the best plan of care?
The “Lingo”

- **SVR**: sustained viral response at 12 weeks after completing antiviral medication. Patients that test negative for virus at week 12 post therapy are considered cured of HCV. Patients with detectable virus after a SVR have been re-infected.

- **DAA**: direct acting antivirals. These are the new generation of HCV meds that followed the interferon era and target specific sites on the HCV genome.

- **Genotype**: there are at least 6 different genotypes of the virus with varying penetration globally.

- **Liver injury**: Stage 4 liver disease represents cirrhosis. Patients can have stage 0-4. Non-invasive tests are available that can obviate the need for a biopsy in many cases.

Global Variance in HCV Genotypes

- 2% ever infected with HCV
- 3.5 million people living in the US with chronic HCV
- 19,658 HCV-related deaths in 2014; may reach 36,000 deaths/year in 2030–2035

1. www.hepatitis.uw.edu/pdf/screening-diagnosis/epidemiology-us/core-concept/all
2. www.cdc.gov/hepatitis/HCV/HCVfaq.htm

Patients with ESRD have a higher prevalence of HCV infection than the general population.

The prevalence of anti-HCV sero-positivity amongst ESRD patients ranges from 5%-20% in developed countries and even higher in less developed regions of the world.

HCV infection is directly involved in the pathogenesis of certain forms of immune-complex GN and cryoglobulinemia and is associated with a higher incidence of CKD and progression to ESRD. HCV-infected kidney transplant recipients have had enormous unmet medical need which is just now being addressed with DAA agents.

Much higher prevalence of HCV infection in CKD and transplant patients than in the general population. Opportunities to treat are now available.
Hepatitis C Virus Infection Increases the Risk for CKD

![Graph showing HR 1.43 (95% CI 1.23;1.63)]

CKD and CVD Outcomes in a Large US Database

- Truven Health MarketScan Database (2008-2014)
- HCV (+) (n=72,213) group with propensity-matched HCV (-) cohort (n=216,639)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR/HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD outcome</td>
<td>2.2</td>
<td>2.01, 2.31</td>
</tr>
<tr>
<td>CVD event</td>
<td>1.91</td>
<td>1.85, 1.97</td>
</tr>
</tbody>
</table>

Association of HCV with the Incidence and Progression of Chronic Kidney Disease

- Cohort study of > 100,000 HCV (+) and > 920,000 HCV (-) US Veterans.
- Associations examined in adjusted Cox models using a propensity-matched cohort for sensitivity analysis.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR/HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2.17</td>
<td>2.13-2.21</td>
</tr>
<tr>
<td>Onset of eGFR &lt; 60 ml/min/1.73m²</td>
<td>1.15</td>
<td>1.12-1.17</td>
</tr>
<tr>
<td>Slope of eGFR loss &gt; 5ml/min/1.73m²</td>
<td>1.22</td>
<td>1.19-1.26</td>
</tr>
<tr>
<td>Development of ESRD</td>
<td>1.98</td>
<td>1.81-2.16</td>
</tr>
</tbody>
</table>
Impact of IFN-based Treatment on the Incidence of CKD

- n=3,679 untreated patients
- n=919 with > 3 mo IFN-based therapy

<table>
<thead>
<tr>
<th>Follow up, year</th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cumulative incidence, %</td>
<td>Modified log rank, p=0.008</td>
</tr>
<tr>
<td></td>
<td>HR=0.42, p=0.03</td>
<td></td>
</tr>
</tbody>
</table>

Untreated
Treated

Impact of HCV Treatment on CKD Progression

- Kaiser-Permanente: HCV-infected patients (n=2,452) treated between 2004-2014.
- CKD defined by eGFR<60 ml/min on 2 measurements > 90 d apart.
- SVR24 achieved in 61.6% using IFN-based and 1st generation DAAs.

<table>
<thead>
<tr>
<th>Patients achieving SVR: HR for ESRD=0.05 (0.01, 0.33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in GFR (ml/min/yr)</td>
</tr>
<tr>
<td>SVR24</td>
</tr>
<tr>
<td>1.12</td>
</tr>
</tbody>
</table>


Antiviral Therapy Impact on the Risk of End-Stage Renal Disease in the HCV-infected Population

Cumulative Incidence of ESRD in a Population (n=37,152) With HCV-infection at Baseline: Differential Effect of Antiviral Therapy

- Hazard ratio for ESRD (HCV antiviral treated/untreated): 0.105 (95% CI, 0.079-0.137) P=0.001

Summary Estimates for All-Cause Mortality Among ESRD Patients: Impact of HCV Infection

<table>
<thead>
<tr>
<th></th>
<th>Fixed effects aRR</th>
<th>Random effects aRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>1.32 (1.25; 1.39)</td>
<td>1.35 (1.25; 1.47)</td>
<td>0.08</td>
</tr>
<tr>
<td>Population-based</td>
<td>1.29 (1.23; 1.36)</td>
<td>1.29 (1.23; 1.36)</td>
<td>0.90</td>
</tr>
<tr>
<td>US studies</td>
<td>1.31 (1.09; 1.56)</td>
<td>1.37 (1.05; 1.78)</td>
<td>0.18</td>
</tr>
<tr>
<td>HD patients only</td>
<td>1.43 (1.23; 1.65)</td>
<td>1.40 (1.21; 1.64)</td>
<td>0.08</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>1.33 (1.26; 1.40)</td>
<td>1.37 (1.27; 1.49)</td>
<td>0.12</td>
</tr>
<tr>
<td>Chronic HCV</td>
<td>1.33 (1.25; 1.40)</td>
<td>1.36 (1.26; 1.46)</td>
<td>0.14</td>
</tr>
<tr>
<td>Non-Australian studies</td>
<td>1.32 (1.24; 1.40)</td>
<td>1.37 (1.24; 1.52)</td>
<td>0.04</td>
</tr>
</tbody>
</table>


Impact of Treatment on Mortality in HCV-Infected Taiwanese ESRD Patients

Survival curve

HR 2.62 (95% CI 1.24-5.55)

Hsu, Ruth-Han; et al. Medicine. 2015;94(47):e2113

HCV Treatment in Dialysis Patients

- IFN and ribavirin in DOPPS 1-4; DAAs used in some of the DOPPS 5 patients

Evolution of HCV Therapies

Sustained virological response rate (%)

- 1980: 7-10%
- 1990: 25%
- 2001: 40-50%
- 2011: 60-70%
- 2014: >90%

Direct-Acting Antivirals

- Peginterferon + ribavirin
- Interferon + ribavirin
- Direct-Acting Antivirals

Direct-Acting Antivirals

NS3/4A inhibitors
- NS3 Serine protease inhibitors
- RNA helicase inhibitors
- RNA polymerase inhibitors
- NS5A inhibitors
- NS5B inhibitors

Potential Therapeutic Targets in the HCV Lifecycle

Structural proteins
- 5' NTR
- 3' NTR
- HCV RNA
- Fusion and uncoating
- RNA replication

Non-structural proteins
- NS2
- NS3
- NS4B
- NS5A
- NS5B
- CypA
- Membrane reorganization
- Phosphoprotein
- Cofactor
- Membrane
- Ion channel
- Transmembrane protein
- Envelope glycoproteins
- Capsid protein
- Regulator of replication and viral assembly

NTR = non-translated region; NS = non-structural protein.
Potential Therapeutic Targets in the HCV Lifecycle

**Does the level of kidney function affect treatment choices in HCV-infected CKD patients?**

**Direct-Acting Antiviral Drug Choices in Patients With Kidney Disease**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary Metabolic Pathway</th>
<th>Recommendations from Package Insert and AASLD Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir</td>
<td>Hepatic</td>
<td>Data not available for CrCl &lt; 30 ml/min</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>Hepatic</td>
<td>No restrictions in CKD or ESRD</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Hepatic</td>
<td>Data not available for CrCl &lt; 30 ml/min</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Hepatic</td>
<td>Limited data for CrCl &lt; 30 ml/min</td>
</tr>
<tr>
<td>Paritaprevir/PI</td>
<td>Hepatic</td>
<td>No dose adjustments necessary for CrCl &lt; 30 ml/min</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Hepatic</td>
<td>No restrictions in CKD or ESRD</td>
</tr>
</tbody>
</table>

**Notes:**
- Sofosbuvir (Sovaldi®) prescribing information (PI); ledipasvir/sofosbuvir (Harvoni®) PI; elbasvir/grazoprevir (Zepatier™) PI.
- No dose adjustments necessary for CrCl < 30 ml/min. Use Ribavirin with caution.
- Hepatic: Hepatic; ESRD/HD: End-stage renal disease/High dialysis.
Studies Providing Data on DAAs in HCV-Infected ESRD Patients

- RUBY-1 (Cohort 1 and 2)
- RUBY-2
- C-SURFER
- EXPEDITION-IV

RUBY-I Study: Ombitasvir/Paritaprevir/ritonavir + Dasabuvir ± RBV for HCV Genotype 1 Patients with CKD

**Design**

- ≥ 18 years old
- Genotype 1
- Treatment-naïve
- CKD 4 (n=6) or 5 (n=14) (all on dialysis)
- No cirrhosis
- No HBV or HIV co-infection

**Results**

- SVR12: 18/20 patients (90%)
- SVR12 in 11/13 (85%) genotype 1a patients
- 9/13 genotype 1a patients had to interrupt ribavirin treatment due to anemia - 4 required EPO.

Vierling JM. AASLD 2016, Abs. 886
RUBY-I Study, Cohort 2: Ombitasvir/paritaprevir/ritonavir + Dasabuvir ± RBV for HCV Genotype 1 with Renal Impairment

Vierling JM. AASLD 2016, Abs. 886

Open label
≥ 18 years
Chronic HCV infection
Genotype 1a or 4
Treatment-naïve
Stage 4 or 5 chronic kidney disease with eGFR (MDRD) < 30 ml/min/1.73m² (dialysis permitted)
No cirrhosis
No HBV or HIV co-infection

RUBY-II Study: Ombitasvir/paritaprevir/ritonavir + Dasabuvir for HCV Genotype 1a or 4 with Stage 4/5/5D CKD

SVR
12
N = 5
Genotype 1a
Genotype 4

N = 13
Genotype 4 (N = 5)
OBV/PTV/r
Genotype 1a (N = 13)
OBV/PTV/r + DSV

C-SURFER: Grazoprevir + Elbasvir in HCV Genotype 1 Patients with CKD 4/5/5D

Objective
SVR with HCV RNA < 15 IU/ml in immediate + PK groups:
40% historical response rate to IFN-based regimens used

C-SURFER: SVR_{12} Rates

SVR_{12} (HCV RNA < 15 IU/ml), % (95% CI), mITT

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Diabetes</th>
<th>mITT</th>
<th>Modified full analysis set</th>
<th>Full analysis set</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0</td>
<td>116</td>
<td>98.3 (95.3-100)</td>
<td>96.3 (95.0-97.7)</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>122</td>
<td>100 (95.2-100)</td>
<td>100 (94.2-100)</td>
</tr>
<tr>
<td>1a</td>
<td>No</td>
<td>61</td>
<td>95.2 (93.8-96.7)</td>
<td>93.0 (91.0-94.9)</td>
</tr>
<tr>
<td>1b</td>
<td>Yes</td>
<td>41</td>
<td>87.6 (82.4-92.9)</td>
<td>90.1 (86.0-93.9)</td>
</tr>
</tbody>
</table>

- Relapse: 0%
- Discontinuation: 1%
- Treatment: 12%
- Genotype 1b, non-cirrhotic, CKD stage 5, NS5A RAV at baseline: L31M, at failure: L31M + Y93H

Modified full analysis set excluded patients who died or discontinued for reasons unrelated to treatment

Expedition-IV: Treatment of HCV-Infected CKD Patients with Glecaprevir and Pibrentasvir

- Single arm
- Open label
- N = 104

- GLE/PIB: 100/40 mg 3 tablets QD

**Objective**

- SVR_{12} (HCV RNA < 15 IU/mL)

- Glecaprevir (NS3/4A inhibitor) and pibrentasvir (NS5A inhibitor) have minimal renal clearance.
- CKD 4: 13%, CKD 5: 87%, 82% HD

Expedition-IV: Treatment of HCV-Infected CKD Patients with Pangenotypic Agents

- 42% TE, 19% comp cirrhosis
- GT1-52%; GT2-16%; GT3-11%; GT4-19%; GT5 and 6-1%

- mITT - 100% SVR_{12}

Gen, et al: AASLD 2016, Ab #1532
Kidney Disease Associated with HCV Infection

Adapted from Soriano, et al. Antiviral Ther 2016;21: 1-8

B-cell Syndromes in HCV-Infected Patients

B-cell proliferation

Mixed Cryptoglobulinaemia/
Glomerulonephritis
Monoclonal gammopathies
Non-Hodgkins lymphomas

Immune-Complex Mediated Injury in HCV-Related Vasculitis

Endothelial activation
Sofosbuvir plus Ribavirin for HCV-Associated Cryoglobulinaemia Vasculitis: The VASCUVALDIC Study

- Open label, prospective study of patients (n=24) with HCV-cryoglobulinaemia vasculitis with skin, joint, renal, peripheral nerve, central neurological, GI, pulmonary and/or cardiac involvement and active HCV viremia.
- Sofosbuvir (400 mg/d) and ribavirin (200-1400 mg/d) x 24 wks.
- Primary efficacy end point: complete clinical response of the vasculitis at the end of treatment defined by improvement of all of the affected organs and the absence of a clinical relapse.
- Renal improvement: proteinuria < 300 mg/24h, disappearance of hematuria and > 20% improvement of GFR at week 24.


<table>
<thead>
<tr>
<th>Variable</th>
<th>CR</th>
<th>PR</th>
<th>Virological response</th>
<th>Cryoglobulin (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>21/24 (87.5%)</td>
<td>3/24 (12.5%)</td>
<td>22/24 (91.7%)</td>
<td>0.15 (0.05-0.45)</td>
</tr>
<tr>
<td>Week 24</td>
<td>20/23 (86.9%)</td>
<td>17/23 (74%)</td>
<td>0 (0-0.37)</td>
<td></td>
</tr>
<tr>
<td>EOT, wk. 12</td>
<td>20/23 (86.9%)</td>
<td>17/23 (74%)</td>
<td>0 (0-0.37)</td>
<td></td>
</tr>
<tr>
<td>Virological failure</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR- complete clinical response; PR- partial response

Kidney Transplantation in the HCV-Infected Patient

What are the Concerns?

1) Effect of immunosuppression on viral replication
2) Impact of HCV infection on:
   - Patient/graft survival
   - Underlying/progressive liver injury
   - Extrahepatic effects
   - HIV co-infection
3) Use of kidneys from HCV+ donors

The Case for Pre and Post Kidney Transplant HCV Therapy

In Favor of Pre
- Cure is probable and durable
- Likely to reduce the risk of:
  - Progressive liver injury
  - Post-transplant GN
  - New onset diabetes
- Avoid drug-drug interactions with IS post transplant

Favoring Post
- Can use HCV’s donor kidney
- Shorter wait time
- Less dialysis vintage
- Improved eGFR of the KTR allows for greater therapeutic options
Control of Viral Replication Improves Patient and Graft Survival Post Kidney Transplantation

- French cohort, 1993-2010
- Viral control: SVR or spontaneous clearance
- HCV infected, n=1109
- Non-infected pts., n=30,602

Treatment of Hepatitis C in Renal Transplant Recipients with Direct Acting Antiviral Agents

Case series of patients who were 1–4 years post-transplant (n=20)
- 88% genotype 1; 60% failed IFN; 45% had HCV+ donor
- 12 weeks follow-up; SVR, 100%
- DAA started mean 88 days post-transplant
- Tacrolimus levels decreased at end of therapy: 45% dose increased

LDV/SOF in Kidney Transplant Recipients

- Objective
  - SVR$_{12}$ (HCV RNA < 15 IU/ml), with 95% CI, by ITT

* Metavir F4 or Ishak ≥ 5 or Fibroscan > 12.5 kPa or Fibrotest > 0.75 and APRI > 2
**Important Considerations When Treating Kidney Transplant Recipients with DAAs**

- Drug-drug interactions: CNIs and mTORi are substrates of CYP3A4/5 and drug transporter P-glycoprotein (P-gp).
- The ideal time to initiate DAA treatment post kidney transplant has not been established.
- Sofosbuvir is not approved for use in patients with eGFR < 30 ml/min/1.73m². Imperative to assess the status of allograft function before starting treatment.
- Possible impact of viral eradication on CNI metabolism.
- Activation of quiescent hepatitis B virus infection

**Summary**

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>HCV Impact</th>
<th>Will antiviral treatment matter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of chronic kidney disease</td>
<td>Yes</td>
<td>Likely</td>
</tr>
<tr>
<td>Increases rate of CKD progression</td>
<td>Yes</td>
<td>Likely</td>
</tr>
<tr>
<td>Increases mortality in ESRD pts</td>
<td>Yes</td>
<td>Possibly</td>
</tr>
<tr>
<td>Increases morbidity in KTR</td>
<td>Yes</td>
<td>Probably</td>
</tr>
<tr>
<td>Transmissible in dialysis clinics</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Case Presentation: Questions

1. What other testing to evaluate the positive HCV ELISA should have been done at initial presentation? Would antiviral treatment have been appropriate at that time?
   
   HCV PCR for viremia. Back then we had IFN- not well tolerated with little data in the CKD area.

2. If presenting today as he did 5 years ago, should this patient be treated with antiviral agents to eradicate his HCV infection?
   
   Data on slowing progression of CKD is intriguing- likely yes.

3. Should the patient be referred for kidney transplantation, sent to see a hepatologist, both or neither at this time?
   
   Yes and yes.

4. Should treatment for HCV be started now? Would post transplant DAA treatment be the best plan of care?
   
   Depends on if LRD is available. If not would hold off and try for HCV positive donor organ.

Thank you! Thank you! Thank you! Thank you!