HCV Treatment as Prevention

Renal Dialysis and Transplantation
"HCV Treatment as Prevention"
Renal Dialysis and Transplantation

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Disclosures

- Advisory Board
  - Bristol Myers Squibb
  - Janssen
  - MSD
  - Gilead
  - Roche
  - Boehringer Ingelheim
  - Achillion

- Speaker’s Bureau
  - GlaxoSmithKline
  - Bristol Myer Squibb
  - MSD
  - Roche
  - Boehringer Ingelheim
  - Gilead
Barriers to HCV eradication

**Screening**
- Screening uptake low

**Diagnosis**
- ELISA, HCV RNA

**Linkage to care**
- Not always linked

**Treatment**
- Availability, cost

**Monitoring**
- Necessary?

**Assess SVR**
- Confirmation needed

Renal Disease/Transplant
- Known population
- Confirmed
- Already on followup
- Cost, efficacy & safety
- Necessary?
- Confirmation needed
How big is the problem?
Meta-analysis of HCV prevalence in Hemodialysis patients in Asia

Based on detection of anti-HCV

Seroprevalance of HCV in US hemodialysis units estimated to be 8-10%

Pooled Estimate = 31% (95% CI 24-38%)

HCV post renal transplant: prevalence

• Multinational Observational Study in Transplantation 1989-2002
• 12,856 kidney transplant recipients in 37 countries

Infection    HBV    HCV
Prevalence    2.9%    8.7%

## Seronegative HCV

<table>
<thead>
<tr>
<th>Population</th>
<th>Seronegative HCV infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/HCV co-infected individuals</td>
<td>3.2–13.2</td>
</tr>
<tr>
<td>Hemodialyzed patients</td>
<td>1–15</td>
</tr>
<tr>
<td>Organ donors</td>
<td>0.2–0.9</td>
</tr>
<tr>
<td>Blood donors</td>
<td>0.0004–0.08</td>
</tr>
</tbody>
</table>

Transmission

HCV outbreaks in Renal Patients
Transmission of hepatitis C virus in dialysis units: a systematic review of reports on outbreaks

- 36 papers reported on 45 outbreaks that involved 335 unique patients on maintenance hemodialysis
- Nosocomial transmission of HCV was confirmed by phylogenetic analysis in most (n = 31; 69%) reports
- Causes:
  - Sharing contaminated hemodialysis machines (18%) and multi-dose vials (13%)
  - Breaches in environmental cleaning and disinfection practices, and failures in medication preparation and administration practices was considered in 65% of outbreaks (exact mechanism unclear)

CDC Report 2008-2014

• HCV: total 22 outbreaks, 239 outbreak-associated cases, >90,400 at-risk persons notified for screening

• 11 outbreaks occurred in hemodialysis settings, with 79 outbreak-associated cases of HCV and 1,833 persons notified for screening
  – Breaches in environment cleaning and hygiene
  – Failure to perform hand hygiene and change gloves
  – Poor disinfection practices
  – Cross contamination between clean and dirty areas
  – Unidentified lapses in infection control
  – Breaches in medication administration

Treatment
PegIFN + RIB for HCV in dialysis patients: meta-analysis of clinical studies

Forrest plot: SVR rate after antiviral therapy

<table>
<thead>
<tr>
<th>Study name</th>
<th>Event rate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruchfeld A</td>
<td>0.500</td>
<td>0.168</td>
<td>0.832</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Rendina A</td>
<td>0.970</td>
<td>0.823</td>
<td>0.996</td>
<td>3.508</td>
<td>0.000</td>
</tr>
<tr>
<td>van Leusen R</td>
<td>0.710</td>
<td>0.324</td>
<td>0.926</td>
<td>1.075</td>
<td>0.282</td>
</tr>
<tr>
<td>Carriero D</td>
<td>0.285</td>
<td>0.111</td>
<td>0.560</td>
<td>-1.554</td>
<td>0.120</td>
</tr>
<tr>
<td>Deltenre P</td>
<td>0.500</td>
<td>0.333</td>
<td>0.667</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Giguere A</td>
<td>0.760</td>
<td>0.510</td>
<td>0.906</td>
<td>2.030</td>
<td>0.042</td>
</tr>
<tr>
<td>Abdulhadi-Al M</td>
<td>0.690</td>
<td>0.407</td>
<td>0.878</td>
<td>1.334</td>
<td>0.182</td>
</tr>
<tr>
<td>Hakim W</td>
<td>0.070</td>
<td>0.010</td>
<td>0.354</td>
<td>-2.556</td>
<td>0.011</td>
</tr>
<tr>
<td>Tseng P</td>
<td>0.620</td>
<td>0.425</td>
<td>0.783</td>
<td>1.212</td>
<td>0.226</td>
</tr>
<tr>
<td>Alsaran K</td>
<td>0.640</td>
<td>0.374</td>
<td>0.841</td>
<td>1.033</td>
<td>0.301</td>
</tr>
<tr>
<td>Liu C</td>
<td>0.640</td>
<td>0.543</td>
<td>0.727</td>
<td>2.803</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>0.600</td>
<td>0.470</td>
<td>0.717</td>
<td>1.508</td>
<td>0.132</td>
</tr>
</tbody>
</table>

Meta Analysis

Pooled estimate = 60% (95% CI 47-72%)

Fabrizi, J Viral Hepatitis 2014;21:681–689
Antiviral Therapy in Renal Transplant Recipients

Pooled estimate for SVR = 27% (95% CI 15-38%)
# DAA Therapy and Renal Clearance

<table>
<thead>
<tr>
<th>Antiviral agent</th>
<th>Dose</th>
<th>Clearance</th>
<th>Dose adjustment (eGFR 15–29 ml/min)</th>
<th>Dose adjustment (eGFR &lt;15 ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>800 mg x3/day</td>
<td>&lt; 10% renal route</td>
<td>Not required</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>750 mg x3/day</td>
<td>1% renal route</td>
<td>Not required</td>
<td>Not studied</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>400 mg/day</td>
<td>81% renal route</td>
<td>Not required</td>
<td>Under investigation</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>150 mg/day</td>
<td>&lt; 1% renal route</td>
<td>Not required</td>
<td>Not investigated</td>
</tr>
<tr>
<td>Grazoprevir/Elbasvir</td>
<td>100/50 mg daily</td>
<td>&lt; 1% renal route</td>
<td>Not required</td>
<td>Not recommended</td>
</tr>
<tr>
<td>3D regimen: ombitasvir, paritaprevir/ritonavir and dasabuvir</td>
<td>25/150/100 mg once daily and 250 mg x2/day</td>
<td>&lt; 2% renal route</td>
<td>Not required</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Ledispavir</td>
<td>90 mg daily</td>
<td>&lt; 1% renal route</td>
<td>Not required</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>30 mg twice daily</td>
<td>&lt; 10% renal route</td>
<td>Not required</td>
<td>30 mg daily</td>
</tr>
<tr>
<td>Asunaprevir</td>
<td>200 mg twice daily</td>
<td>&lt; 10% renal route</td>
<td>Not required</td>
<td>200 mg daily</td>
</tr>
<tr>
<td>Beclabuvir</td>
<td>75 mg twice daily</td>
<td>&lt; 10% renal route</td>
<td>Not required</td>
<td>75 mg daily</td>
</tr>
</tbody>
</table>

How many patients on hemodialysis have been treated?

• The Dialysis Outcomes and Practice Patterns Study

• 49,762 HD patients in 12 nations enrolled between 1996 and 2011

• 9.5% (n=4,735) were HCV+ but only 1% (n=48) received antiviral treatment (PR)

**RUBY-1: OBV/PTV/RTV + DSV ± RBV in Tx-naive, Noncirrhotic GT1 Pts With CKD**

- Multicenter, open-label phase IIIb study

Tx-naive, noncirrhotic GT1 pts with eGFR < 30 mL/min/1.73m²
(N = 20)

- Key baseline characteristics
  - F3 fibrosis: 20%; eGFR 15-30: 30%; eGFR < 15 or on dialysis: 70%
  - 2 pts without SVR12: 1 relapsed, 1 died of LV systolic dysfunction, cardiac arrest after treatment completion
  - 69% of pts with GT1a required RBV dose reduction for anemia
    - No discontinuations for anemia
  - No cases of grade 3 or higher ALT elevations

*RBV dosed at 200 mg QD and managed as follows: RBV dosed 4 hrs before hemodialysis in hemodialysis pts; wkly Hb assessment in Mo 1 and then Wks 6, 8, 12; RBV suspended in pts with > 2 g/dL decline in Hb in < 4 wks or Hb < 10 g/dL; RBV dosing resumed at clinician’s discretion if Hb normalized.

**GT1a: OBV/PTV/RTV + DSV + RBV**

**GT1b: OBV/PTV/RTV + DSV**

12 Wks  
SVR12, % (n/N)

90 (18/20)

Most common adverse events were headache, nausea, and fatigue, occurring at similar frequencies in patients receiving active and placebo drugs.

*Modified analysis set: pts in pharmacokinetic substudy and pts randomized to immediate treatment who received ≥ 1 drug dose; excludes pts who died or discontinued where cause not related to study treatment.
†Full analysis set: all pts receiving ≥ 1 drug dose.

HCV DAA Treatment in Renal Transplant patients

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>N</th>
<th>DAA combination</th>
<th>Duration (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2</td>
<td>Sofosbuvir + ledipasvir</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Pegylated interferon + ribavirin +</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sofosbuvir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Sofosbuvir + simeprevir</td>
<td>12</td>
</tr>
<tr>
<td>1b</td>
<td>5</td>
<td>Sofosbuvir + simeprevir</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Sofosbuvir + ledipasvir</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Sofosbuvir + daclatasvir</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Sofosbuvir + ledipasvir + ribavirin</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Sofosbuvir + simeprevir + ribavirin</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Sofosbuvir + ribavirin</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Sofosbuvir + ribavirin</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>Sofosbuvir + ledipasvir</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Sofosbuvir + daclatasvir</td>
<td>12</td>
</tr>
</tbody>
</table>

- n=25
- SVR12 = 100%
- No SAEs
- No change in immunosuppression

Kamar, Am J Transplantation 2015; epub ahead of print
HCV Outbreak in Renal Transplant patients in Singapore

Summary

Between April – Sept 2015, there was an outbreak of 25 cases of acute HCV in the renal unit of a major tertiary hospital in Singapore.

- 22/25 patients were renal transplant patients.
- There were 8 deaths, 7 of whom were attributed to HCV, likely to be fibrosing cholestatic hepatitis.

Sequence of outbreak cases

Findings of the Outbreak Committee

Members
• Singapore investigating committee
• US CDC
• Johns Hopkins

• Multidose vials were excluded as a source
• Drug diversion was excluded
• Infection control lapses identified as the likely source
  – Use of trolleys
  – Complex infection control practices
  – Shortcuts taken by staff

Blood splatter on a medication cart

Salient learning points

- HCV in renal transplant patients had viral loads > upper limit of detection (>10⁸ IU/ml)
- This translates into >50 x 10⁶ IU/ml per drop of blood (50 µl)
- Small amounts of blood can lead to high environmental contamination
- HCV RNA was isolated from a clean room 4m after the outbreak

- HCV RNA can be isolated from dried blood spots after 1 year in experimental conditions
- Dried blood spots can infect Chimpanzees after 16h but not after 4 or 7 days
- Using a luciferase reporter assay, dried blood spots were infective up to 6 weeks in experimental conditions

Bennett, J Clin Virology 2012;54:106–109
Paintsill, J Inf Dis 2014;209:1205–11
Guideline recommendations on HCV in dialysis patients
3.1 HD units should ensure implementation of, and adherence to, strict infection-control procedures designed to prevent transmission of blood-borne pathogens, including HCV. (Strong)

- Isolation of HCV-infected patients is not recommended as an alternative to strict infection-control procedures for preventing transmission of blood-borne pathogens. (Weak)
- The use of dedicated dialysis machines for HCV-infected patients is not recommended. (Moderate)
- When dialyzer reuse is unavoidable, it is suggested that the dialyzers of HCV-infected patients can be reused provided there is implementation of, and adherence to, strict infection-control procedures. (Weak)

3.2 Infection-control procedures should include hygienic precautions that effectively prevent the transfer of blood or fluids contaminated with blood between patients, either directly or via contaminated equipment or surfaces. (Strong)

- It is suggested to integrate regular observational audits of infection-control procedures in performance reviews of HD units. (Weak)
Persons on hemodialysis:

• The prevalence rate of HCV infection is markedly elevated in persons on hemodialysis and ranged from 2.6% to 22.9% in a large multinational study. Studies in the United States found a similarly elevated prevalence rate of 7.8% to 8.9%. (HCV-infected persons on hemodialysis have a decreased quality of life and increased mortality compared with uninfected persons on hemodialysis. Importantly, the seroprevalence of HCV was found to increase with time on dialysis, suggesting that nosocomial transmission, among other risk factors, plays a role in HCV acquisition in these patients. Improved education and strict adherence to universal precautions can drastically reduce nosocomial HCV transmission risks for persons on hemodialysis but clearance of HCV viremia through treatment-induced SVR eliminates the potential for transmission.

• HCV-infected persons on hemodialysis have a decreased quality of life and increased mortality compared with uninfected persons on hemodialysis. HCV infection in this population also has a deleterious impact on kidney transplantation outcomes with decreased patient and graft survival. The increased risk for nosocomial transmission and the substantial clinical impact of HCV infection in those on hemodialysis are compelling arguments for HCV therapy as effective antiviral regimens that can be used in persons with advanced renal failure become available.
Editorial, Lancet Oct 2015 based on C-Surfer study
Towards eradication of hepatitis C virus from dialysis units

• it is now time to envision eradication of HCV from such units. Needless to say, this goal should best be achieved by the combination of prevention and cure, rather than by cure only. The long-awaited availability of highly active anti-HCV drugs should be no reason for complacency regarding the application of basic cost-effective hygiene precautions within haemodialysis units

Michel Jadoul, Yves Horsmans
Departments of Nephrology and Hepatogastroenterology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, B-1200 Brussels, Belgium
Discussion points

• Should HCV in renal dialysis and transplant patients be treated to eradicate and prevent transmission?

• What treatment regimens are appropriate?
  – Advanced renal disease not on dialysis
  – Patients on hemodialysis
  – Patients who have been transplanted