Updates in Transplantation: Current Challenges in Caring for the Hepatitis C Virus Positive Patient

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Pennsylvania Hospital
Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
Objectives

• Describe the outcomes of solid organ transplantation in patients with hepatitis C virus (HCV)
• Assess the advantages and disadvantages of initiating treatment for HCV in a pre-transplant candidate
• Select and recommend HCV treatment for a solid organ transplant recipient
• Design an immunosuppression regimen for a transplant recipient with HCV
Hepatitis C Virus (HCV) Prevalence

Centers for Disease Control and Prevention. Division of Viral Hepatitis. Statistics and Surveillance
HCV in Transplantation

Liver Transplant Wait-List

Liver Transplants Performed

OPTN/SRTR 2016 Annual Data Report: Liver, Volume: 18, Issue: S1, Pages: 172-253,
First published: 02 January 2018, DOI: (10.1111/ajt.14559)
Patient and Graft Survival

Deceased Donor Liver Transplant

Patient Survival

Graft Survival

Where We Are Now

Organ wait list shortcut: Patients accepting kidneys, hearts infected with hepatitis C

Meeting Coverage > EASL

Hepatitis C Treatments Reduce Transplants

— Therapies also appear to reduce liver-related mortality

by Ed Susman, Contributing Writer, MedPage Today
April 15, 2018

New Hepatitis C Drugs Mean More Organs For More Transplants

It's now safe for transplant patients to receive organs from donors with hepatitis C.
KEY TAKEAWAYS

1) Patient and graft survival outcomes are expected to greatly improve for transplant recipients with HCV based upon new therapies

2) Over the next decade, HCV is expected to no longer be a top indication for liver transplantation
To Treat or Not to Treat?
Considerations for Transplant Candidates

Srijana Jonchhe, Pharm.D., BCPS
Clinical Pharmacy Specialist- Liver Transplant
University Hospital New Jersey
Objective

• Assess the advantages and disadvantages of initiating treatment for HCV in a pre-transplant candidate
Patient Case

Patient JB is a 52 yo AA male who presents to hepatology clinic for his initial transplant evaluation appointment. He states he was informed of his hepatitis C infection after his primary care physician noted increased LFTs during routine blood work.

PMH: HCV cirrhosis c/b portal hypertension, history of IV drug abuse (last used 2009), anxiety, hyperlipidemia
Ht: 5’10”
Wt: 94 kg

Labs: Pending
HCV genotype: 1b
HCV viral load (7/2018): 62,240 copies/mL
Liver Transplant Candidates

- Up to 85% with acute HCV infection develop chronic HCV infection
  - Approximately 15-30% progress to cirrhosis over 20 years

- HCV-related cirrhosis risks:
  - End stage liver disease
  - Hepatocellular carcinoma (HCC)

- Chronic HCV infection is a leading indication for liver transplant (LT)
A New Era: Direct Acting Antivirals (DAA)

- Better safety/tolerability than interferon-based regimens
- Shorter treatment duration
- Improved efficacy
- Fewer drug-drug interactions
- Growing literature in transplant

Cleveland Clinic Journal of Medicine, 81 (3): 159-172
<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Year Approved</th>
</tr>
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<tbody>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>Mavyret</td>
<td>2017</td>
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<tr>
<td>Sofosbuvir/Velpatasvir/Voxilaprevir</td>
<td>Vosevi</td>
<td>2017</td>
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<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>Epclusa</td>
<td>2016</td>
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<tr>
<td>Elbasvir/Grazoprevir</td>
<td>Zepatier</td>
<td>2016</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Daklinza</td>
<td>2015</td>
</tr>
<tr>
<td>Ombitasvir/Paritaprevir/ritonavir + Dasbuvin</td>
<td>Viekira pak</td>
<td>2014</td>
</tr>
<tr>
<td>Ledipasvir/Sofobuvir</td>
<td>Harvoni</td>
<td>2014</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Sovaldi</td>
<td>2013</td>
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<tr>
<td>Simeprevir</td>
<td>Olysio</td>
<td>2013</td>
</tr>
</tbody>
</table>
Post-transplant HCV

- Universal HCV recurrence
- Rapid progression to cirrhosis
- Fibrosing cholestatic hepatitis (FCH)
- Worse graft and patient survival

Thuluvath PJ. Am J Transplant 2010
Forman LM. Gastroenterology 2002
## Outcomes of DAA Treatment Pre-Transplant

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curry et al. Gastroenterology 2015</td>
<td>Phase 2, open label study of 61 HCV/HCC patients awaiting liver transplant</td>
<td>Up to 48 weeks of SOF/RBV before transplant</td>
<td>N= 43 transplanted with HCV RNA &lt; 25 IU/ml at time of transplant</td>
<td>Recurrence (10%) inverse to number of days undetectable HCV RNA before transplant MELD exception points</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-transplant virologic response at 12 weeks = 75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlton et al. Gastroenterology 2015 (SOLAR-1)</td>
<td>Phase 2, multicenter, open label study including patients with decompensated cirrhosis</td>
<td>12 vs. 24 weeks of ledipasvir/SOF + RBV in patients with moderate and severe hepatic impairment</td>
<td>N= 108 SVR rate = 87-89% MELD and CTP scored decreased</td>
<td>Lack of long-term follow up Adverse effects mostly related to ribavirin</td>
</tr>
</tbody>
</table>

SOF: sofosbuvir; RBV: ribavirin
Achieving SVR

- ↓ All-cause mortality
- ↓ Liver related complications
- ↓ Need for transplant
- ↓ Rates of HCC
- ↓ Extra-hepatic manifestations

Lee MH. J Infect Dis. 2012
Van der Meer. Journal of Hepatology 2016
Mahale P et al Gut. 2018
Patient Case

JB returns to hepatology clinic 3 months later after recently being discharged from the hospital. He states his abdomen was “swelling like a balloon.” Therapeutic paracentesis was performed (3 L removed)

PMH: HCV (1a) cirrhosis c/b portal hypertension and ascites, history of IV drug abuse (last used 2009), anxiety, hyperlipidemia
Patient Case

Home Medications:
- Hydroxyzine 25 mg PO QHS
- Bupropion 100 mg PO daily
- Furosemide 40 mg PO daily
- Propranolol 10 mg PO BID
- Omeprazole 20 mg PO daily
- Spironolactone 100 mg PO daily

Labs: sCr 1.3, bilirubin 1.9, INR 1.4
- AST: 52
- ALT: 47
- Alk Phos: 109

Transplant status: listed
MELD score = 17
CTP score = A

MELD: Model of End Stage Liver Disease; CTP: Child-Turcotte Pugh
Organ Allocation: Liver Transplant

- Model of End Stage Liver Disease (MELD) score
  - Used to allocate livers to adult transplant recipients
  - Affected by: bilirubin, INR, serum creatinine and sodium
“MELD Purgatory?”

Decompensated HCV+ Liver transplant candidate

HCV treatment with SVR12

↓ MELD score

Longer wait time
Poor quality of life

Decompensated HCV- Liver transplant candidate

Ascites and hepatic encephalopathy unchanged

UNOS Liver Allocation Policy 2017
Gastroenterology. 2003;124:91-6
HCV Treatment Pre Vs. Post Liver Transplant

- Optimal MELD threshold
- Cost-effectiveness
- Quality of life-years

Chhatwal et al. Hepatology 2017

Flemming J. Hepatology 2017
Samur S et al. Clin Gastroenterol Hepatol 2018
The ongoing debate...

Cholankeril G et al. J Clin Transl Hepatol 2017

Verna EC. Hepatology 2017
## Special Considerations

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Class</th>
<th>Decompensated cirrhosis</th>
<th>CKD Stage 4 or 5</th>
<th>Genotype</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>NS5A NS3/4A</td>
<td>X</td>
<td>12 weeks</td>
<td>1a, 1 b, 4</td>
<td>I B</td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>NS5A NS3/4A</td>
<td>X</td>
<td>8-16 weeks</td>
<td>1-6</td>
<td>I B</td>
</tr>
<tr>
<td>Ledipasvir/ Sofobuvir</td>
<td>NS5A NS5B</td>
<td>12 weeks (RBV) 24 weeks (no RBV)</td>
<td>X</td>
<td>1,4,5,6</td>
<td>I A</td>
</tr>
<tr>
<td>Daclatasvir/Sofosbuvir</td>
<td>NS5A NS5B</td>
<td>12 weeks (RBV) 24 weeks (no RBV)</td>
<td>X</td>
<td>1-4</td>
<td>II, B, II C</td>
</tr>
<tr>
<td>Velpatasvir/Sofosbuvir</td>
<td>NS5A NS5B</td>
<td>12 weeks (RBV) 24 weeks (no RBV)</td>
<td>X</td>
<td>1-6</td>
<td>I A</td>
</tr>
</tbody>
</table>

**AASLD/IDSA HCV guidelines- updated 9/2017**
Patient Case

What would be an appropriate treatment strategy for patient JB’s HCV?

A. Hold HCV treatment until after patient receives a liver transplant
B. Start treatment with ledipasvir/sofobuvir/ribavirin for 12 weeks. Extend therapy to 24 weeks if unable to tolerate ribavirin
C. Start treatment with sofosbuvir 400 mg/ribavirin 600 mg daily for up to 48 weeks prior to transplant
D. Inform patient he will not benefit from DAA therapy due to severe decompensated cirrhosis
Pre-Transplant Treatment

- Improved graft outcomes
- Reduce all-cause mortality
- Alleviate need for transplant
- Less drug interactions - no immunosuppression

- Longer wait time without HCV donor pool
- Risk of reinfection
- Treatment failure/resistance
- Limited treatment options
- Potential peri-transplant treatment concerns
Decision to treat

- Anticipated time to transplant
- Degree of liver disease
- Treatment options
Renal
Heart
Lung
Other: small bowel, pancreas
Renal Transplant Candidates

- HCV is independently associated with chronic kidney disease
  - 5-10 % in HD units
  - Higher mortality

- HCV in renal transplant recipients increases risk of:
  - ↑ Graft loss
  - ↑ Liver-related complications (cirrhosis, FCH, HCC)
  - ↑ Infection, Diabetes
  - ↑ Death

Fabrizi F. Am J Transplant. 2014
Finelli L. Semin Dial 2005
Renal Transplant Candidates

• KDIGO guidelines recommend evaluating *all* chronic kidney disease patients for HCV treatment

• Treatment pre-transplant was previously limited by genotype due to lack of safety data in ESRD
  – C-SURFER
  – EXPEDITION-4
Renal Transplant Candidates

• KDIGO guidelines recommend evaluating *all* chronic kidney disease patients for HCV treatment

• Treatment pre-transplant was previously limited by genotype due to lack of safety data in ESRD
  – C-SURFER
  – EXPEDITION-4

• *Kidney transplant candidates with HCV are also eligible to receive HCV positive organs, shortening the wait time significantly in some regions*
**Special Considerations**

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<td>I/II, B, II C</td>
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<tr>
<td>Velpatasvir/Sofosbuvir (Epclusa ®)</td>
<td>12 weeks (RBV) 24 weeks (no RBV)</td>
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AASLD/IDSA HCV guidelines- updated 9/2017
Cardiac Transplant Candidates

- Prevalence of HCV appears to be similar to general population (~2%)

2016 ISHLT listing criteria for heart transplantation:
- Contraindicated if signs of cirrhosis, portal hypertension, or HCC
- Liver biopsy should be performed
- Anti-viral treatment should be considered

Lee et al. J Heart Lung Transplant 2011
Gasinki et al. JAMA 2006
Lung Transplant Candidates

- Prevalence of HCV appears to be similar to general population (~2%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design*</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
</table>
1 yr: 84.7% vs 82%  
3 yr: 63.9% vs 65%  
5 yr: 49.4% vs 51.4% | Most HCV+ patients were probably not viremic |
| Englum BR. J Heart Lung Transplant 2016    | Retrospective, multicenter, lung transplant recipients from 1994-1999 and 2000-2011 | Overall survival lower in HCV+ during the early era but not in recent era  
Median: 1.7 vs 4.5 years; p=0.004  
4.4 vs 5.4 years; p = 0.100 | Recent era based on improved HCV treatment options |

* Both studies utilized OPTN/UNOS database
Relative Contraindication:
“Lung transplant can be considered in patients without significant clinical, radiologic, or biochemical signs of cirrhosis or portal hypertension and who are stable on appropriate therapy.”
Pre-Transplant Treatment

- Improved graft outcomes
- Reduce all-cause mortality
- Alleviate need for liver transplant
- Less drug interactions - no immunosuppression

- Longer wait time without HCV donor pool
- Risk of reinfection
- Treatment failure/resistance
- Limited treatment options
- Potential peri-transplant treatment concerns
Decision to Treat Pre-transplant

Time to transplant
- MELD score
- Regional HCV+ donor prevalence
- Living donor options
- Transplant acuity

Signs/symptoms of liver disease
- CTP score
- Fibrosis score
- Compensated vs. decompensated

Treatment options
- Renal impairment
- Hepatic impairment
- Genotype
KEY TAKEAWAYS

1) With the advent of DAAs, treatment of HCV in pre-transplant candidates can reduce liver-related complications, improve patient survival and prolong graft survival

2) The benefits of achieving SVR pre-transplant should be weighed against the potential disadvantages of a longer wait time for non-HCV organs, especially in patients where liver transplant is required to improve quality of life

3) Treating HCV early may alleviate the need for transplant in select liver candidates, allowing for more effective utilization of organs while providing long term cost benefits
Resources for HCV treatment

- AASLD/IDSA guidelines: https://www.hcvguidelines.org
- World Health Organization Guidelines for Hepatitis C (July 2018)
- KDIGO Clinical Practice Guideline (February 2017)
- Drug interactions: https://www.hep-druginteractions.org
Updates in Transplantation: Current Challenges in Caring for the Hepatitis C Virus Positive Patient

Vicky Kuo, Pharm.D.
Clinical Pharmacist, Solid Organ Transplantation
University of California, San Francisco
Objectives

• Compare the risks and benefits of utilizing HCV positive organ donors
HCV Positive Organ Donor Utilization (2010-2014)

**Donated HCV + Organ Donors**
- 1812 HCV + donors
- Age < 40
- Donated at least 1 organ

**Discarded HCV + Organ Donors**
- Kidneys: 2075
- Livers: 382
- Lungs: 2980
- Hearts: 1069

Concerns with Utilizing HCV Positive Organ Donors
Pre-DAA Era

Disease Transmission

Complications

- Reduced patient and graft survival
- Rapid progression of liver fibrosis
- Increased risk of acute rejection, graft complications
- HCV treatment failure
Use of HCV Positive Organs in HCV Negative Transplant Recipients

Adapted from Gonzalez SA et al. Hepatology 2018; 67: 1600-08.
## Opioid Epidemic

| Population | • Persons who inject drugs  
| • Young (age 20-40), white race with few other medical comorbidities |

| Increase in Deaths | • 3 fold increase in drug overdose related deaths  
| • In 2014, 47,000 deaths related to drug overdose |

| Increase in Donor Pool | • 17% increase per year in overdose death donors  
| • Resulting in 13% of donor pool |

---

HCV “Positive” Donor

- HCV seropositive, NAT negative (nonviremic)
  - Spontaneous clearance of HCV
  - Successfully treated infection
  - False positive antibody

NAT = nucleic acid testing

Does not result in HCV transmission and is deemed safe to use

Quality of HCV Nonviremic Organs

<table>
<thead>
<tr>
<th>Methods</th>
<th>Retrospective case-control analysis of UNOS data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Organ donors from DDRTs performed Dec 2014-2016</td>
</tr>
<tr>
<td>Donor Characteristics</td>
<td>Recipient Characteristics</td>
</tr>
<tr>
<td>• Younger</td>
<td>• Older, male, black race, HCV+, diabetic, previous transplant</td>
</tr>
<tr>
<td>• lower SCr, hypertension,</td>
<td>• Lower PRA, reduced days on dialysis and waitlist</td>
</tr>
<tr>
<td>diabetes, DCD</td>
<td></td>
</tr>
<tr>
<td>• White race, PHS increased</td>
<td></td>
</tr>
<tr>
<td>risk designation</td>
<td></td>
</tr>
</tbody>
</table>

SCr = serum creatinine, DCD = donation after cardiac death, PHS = Public Health Service, PRA = panel-reactive antibody

# Quality of HCV Nonviremic Organs

## Methods

Retrospective case-control analysis of UNOS data
Organ donors from DDRTs performed Dec 2014-2016

## Findings

<table>
<thead>
<tr>
<th>Findings</th>
<th>HCV Ab-, NAT- (N=19,633)</th>
<th>HCV Ab+, NAT- (N=205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Survival</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>Acute Rejection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft Survival</td>
<td>92.2 ± 0.1% (P=0.08)</td>
<td>96 ± 0.02%</td>
</tr>
<tr>
<td>Incidence of DGF</td>
<td>33.9% (P&lt; 0.0001)</td>
<td>19%</td>
</tr>
</tbody>
</table>

HCV “Positive” Donor

- HCV seropositive, NAT positive (viremic) = active infection
- HCV seronegative, NAT positive (viremic) = acute infection
  - Within 2 months of exposure

Potentially providing 300-500 donation opportunities per year

HCV Positive Transplant Recipients

Patient and graft survival is lower in those who receive HCV positive donors when compared to those who receive HCV negative donors

A TRUE
B FALSE
Liver Transplant

- Older donor age and donors with significant fibrosis were found to have faster HCV recurrence

Northup PG et al. Transpl Intl 2010;23:1038-44.
# Renal Transplant

**Methods**
Observational, two-centers
Transplanted 1990-2007 (N=468 HCV+ recipients)
Group 1 HCV+ donors (N=162); Group 2 HCV- donors (N=306)

<table>
<thead>
<tr>
<th>Findings*</th>
<th>Patient Survival</th>
<th>Graft Survival (P=0.006)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year (Group 1 vs. 2)</td>
<td>84.8% vs. 86.6%</td>
<td>58.9% vs. 65.5%</td>
</tr>
<tr>
<td>10 year (Group 1 vs. 2)</td>
<td>72.7% vs. 76.5%</td>
<td>34.4% vs. 47.6%</td>
</tr>
<tr>
<td>Acute rejection 42% vs. 37%; NODAT 21% vs. 12.4% (P= 0.03); HCV-related glomerulonephritis 6.8% vs 7.2%</td>
<td></td>
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</tr>
</tbody>
</table>

*Donor HCV + serology did not significantly increase risk of death, graft loss, decompensated liver disease, or incidence of NODAT

Renal Transplant

<table>
<thead>
<tr>
<th>Methods</th>
<th>Scientific Registry of Transplant Recipients (SRTR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV+ recipients transplanted between 1995-2009 (N=6830)</td>
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<tr>
<td></td>
<td>Receiving HCV+ vs. HCV- donors</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Findings</th>
<th>Patient Survival</th>
<th>HR 1.29 (p&lt;0.001)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1% difference at 1 year survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2% difference at 3 year survival</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Graft Survival</th>
<th>HR 1.18 (p=0.007)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No difference at 1 year survival</td>
</tr>
<tr>
<td></td>
<td>3% difference at 3 year survival</td>
</tr>
</tbody>
</table>

Accepting HCV+ donor ↓ average waitlist time by 395 days

Lung Transplant

Englum BR et al. JHLT 2016; 35: 228-35.

1994

Use of HCV+ Donors: 0.73%

Patient Survival (PS): 1.3 (HCV+ Donor) vs. 4.5 years (HCV- Donor) \((P=0.004)\)

2000

Use of HCV+ Donors: 0.06%

PS: 4.4 (HCV+ Donor) vs. 5.4 years (HCV- Donor)

2011
HCV Positive Organ Donors in HCV Positive Recipients

- **Liver**
  - Similar patient and graft survival
  - Use of HCV+ organs is acceptable

- **Kidney**
  - Improved survival compared with waitlist mortality
  - Use of HCV+ organs is generally acceptable

- **Thoracic**
  - Limited data from pre-DAA era
  - Reduced patient and graft survival compared to HCV- organs, variability in complications
  - HCV+ organs discarded at high rates
HCV Negative Transplant Recipients

HCV negative recipients receiving HCV positive organ donors have a higher risk of acute rejection and reduced patient and graft survival

A  TRUE
B  FALSE
Liver Transplant

• No available data on the use of HCV + livers in HCV - recipients
  – Concern for risk of rapidly progressive fibrosis and HCV-related disease

• Modeling Study:
  – Projecting a possible benefit in reduced wait time by accepting HCV + organ in HCV - recipients with MELD > 20
  – Highest benefit observed at MELD of 28
  – Model analysis can help inform future trial study design

Renal Transplant Key Trial: THINKER

Methods
Prospective, open-label, single center
Recipients: HCV NAT -, age 40-65 (N=20)
Donors: HCV NAT+, genotype 1a or 1b

Findings
- All recipients achieved SVR12
- No treatment related adverse events
- Excellent allograft function
- No cases of acute rejection at 6- and 12- month follow-up
- Time to transplant: 57 days (12-91 days)

DAA used: elbasvir/grazoprevir

Goldberg DS et al. NEJM 2017;376;24:2394-5.
Renal Transplant Key Trial: EXPANDER

<table>
<thead>
<tr>
<th>Methods</th>
<th>Prospective, open-label, single center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipients:</td>
<td>HCV NAT -, age ≥ 50 (N=10)</td>
</tr>
<tr>
<td>Donors:</td>
<td>HCV NAT+, all genotypes</td>
</tr>
</tbody>
</table>

| Findings                 | • Median KDPI: 45% (41-50%)             |
|                          | • No treatment related adverse events   |
|                          | • No acute rejection at 6 month follow-up|
|                          | • Median time to transplant: 1 month (0.7-2 months) |

DAA used: elbasvir/grazoprevir; addition of sofosbuvir if donor was genotype 3

Cardiac Transplant

<table>
<thead>
<tr>
<th>Methods</th>
<th>Retrospective case series, single-center N=13, n=9 treated; 6 month follow-up</th>
</tr>
</thead>
</table>
| Findings                      | • Mean donor age: 29 ± 6 years  
• Waitlist time: 11 ± 12 days (total time 256 ± 583 days)  
• Mean time to DAA initiation: 47 days (26-95 days)  
• 4 of 13 did not develop HCV infection  
• 8 of 9 achieved SVR12, 1 died of pulmonary embolism  
• No SAEs, drug interactions or delays in obtaining DAA medication noted |

DAA used: ledipasvir/sofosbuvir; velpatasvir/sofosbuvir if donor genotype 3
SAEs = serious adverse events

## Lung Transplant

<table>
<thead>
<tr>
<th>Methods</th>
<th>Case report, genotype 1a</th>
<th>Case series, genotype 1, 2 (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to transplant</td>
<td>Not reported</td>
<td>51 days (24-94)</td>
</tr>
<tr>
<td>Time to DAA initiation</td>
<td>6 weeks post transplant</td>
<td>24-94 days post transplant</td>
</tr>
<tr>
<td>Safety</td>
<td>No SAEs or acute rejection</td>
<td>No SAEs or acute rejection</td>
</tr>
</tbody>
</table>

DAA used: ledipasvir/sofosbuvir; ledipasvir/sofosbuvir or velpatasvir/sofosbuvir

HCV Negative Recipients

• Further studies needed to assess use in HCV negative liver recipients

• Short term data with DAA treatment show high rates of HCV cure (SVR12) with good graft function and minimal side effects

• Further studies needed to assess long term data on graft and patient survival, risk of rejection, in addition to complications associated with HCV infection
Considerations for Utilizing HCV Positive Organ Donors in HCV Negative Recipients

• Risk of clinical deterioration while waiting for HCV- organ offer
• Age
• Prolonged waitlist time
• No available living donors
• No substantial risk for liver disease
• Clinical trial opportunities
Ethical Perspective

- Mismatch between organ supply and demand
- Patient willingness
- Multistep informed consent process
- Cost and obtaining DAA medication

Patient Willingness to Accept HCV Positive Organs

• Survey with different scenarios from each category

Donor Kidney Quality

- A. 20 year old
- B. 60 year old + hypertension

HCV Cure Rate Post Transplant

- A. 75%
- B. 90%
- C. 95%

Wait Time for HCV - Offer

- A. 2 years
- B. 5 years

Patient Willingness to Accept HCV Positive Organs

- Willingness to accept HCV positive organ
  - Under all circumstances: 53%
  - At least one circumstance: 82%
  - 18% refused all offers

- Participants highly influenced by anticipated HCV cure rate and better allograft quality

- Participant attributes associated with willingness to accept offer
  - Age > 60, transplant reevaluation, prior transplant recipient

- Most patients acknowledged limited understanding of HCV

Multi-step Patient Consent Approach

Describe HCV, risk of HCV, and possible complications

Potential Benefits: Reduced wait time vs. risk of death or health deterioration on wait list

Communicate possible adverse consequences: Treatment or graft failure risks, side effects

Cost: inform possibility of high cost or insurance approval for DAA therapy not guaranteed

Medication Approval and Cost Considerations

• Hepatology consult

• Obtaining appropriate documentation to initiate HCV treatment request
  – Requested information may vary based on insurance plan

• Cost to the patient
  – Financial counseling
  – Patient assistance programs, contingency plan vs. patients pay out of pocket
  – Insurance plan formulary

Goldberg DS et al. NEJM 2017;376;24:2394-5.
## Utilization of HCV + Donors

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increase donor pool</td>
<td>• Disease transmission</td>
</tr>
<tr>
<td>• Better donor quality</td>
<td>• Treatment cost and availability</td>
</tr>
<tr>
<td>• Decrease time on waitlist</td>
<td>• Concern for</td>
</tr>
<tr>
<td>• Decrease waitlist mortality</td>
<td>• treatment failure</td>
</tr>
<tr>
<td>• High cure rate with DAA treatment</td>
<td>• DAA resistance</td>
</tr>
<tr>
<td></td>
<td>• HCV associated complications</td>
</tr>
<tr>
<td></td>
<td>• increased morbidity &amp; mortality</td>
</tr>
<tr>
<td></td>
<td>• Societal barriers</td>
</tr>
</tbody>
</table>

KEY TAKEAWAYS

1) HCV positive organs are currently being underutilized. These donors are otherwise young with minimal or no other medical comorbidities.

2) Utilizing HCV positive organs can decrease time on waitlist and possible waitlist mortality. These grafts show good short term outcomes.

3) Larger, prospective clinical trials are needed to assess long term data of HCV impact on complications, patient and graft survival, as well as treatment failure.
Updates in Transplantation: Current Challenges in Caring for the Hepatitis C Virus Positive Patient

Kimberly Boyle, Pharm.D., BCPS
Cardiothoracic Transplant Clinical Pharmacist
Vanderbilt University Medical Center
Objectives

- Select and recommend HCV treatment for a solid organ transplant recipient
- Evaluate pertinent drug interactions relevant to HCV treatment in solid organ transplant patients
- Design an immunosuppression regimen for a transplant recipient with HCV
HCV Treatment

- Allograft Function
- Drug Interactions
- Genotype
- Patient-Specific Factors
<table>
<thead>
<tr>
<th>Therapy Selection: Allograft Function &amp; Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elbasvir/Grazoprevir (Zepatier ®)</strong></td>
</tr>
<tr>
<td>Genotype: 1, 4</td>
</tr>
<tr>
<td>Use in Hepatic Impairment: Mild</td>
</tr>
<tr>
<td>Use in Renal Impairment: Yes</td>
</tr>
<tr>
<td><strong>Glecaprevir/Pibrentasvir (Mavyret ®)</strong></td>
</tr>
<tr>
<td>Genotype: 1-6</td>
</tr>
<tr>
<td>Use in Hepatic Impairment: Mild</td>
</tr>
<tr>
<td>Use in Renal Impairment: Yes</td>
</tr>
<tr>
<td><strong>Ledipasvir/ Sofobuvir (Harvoni ®)</strong></td>
</tr>
<tr>
<td>Genotype: 1,4,5,6</td>
</tr>
<tr>
<td>Use in Hepatic Impairment: Yes</td>
</tr>
<tr>
<td>Use in Renal Impairment: CrCl ≥ 30ml/min</td>
</tr>
<tr>
<td><strong>Velpatasvir/sofosbuvir (Epclusa ®)</strong></td>
</tr>
<tr>
<td>Genotype: 1-6</td>
</tr>
<tr>
<td>Use in Hepatic Impairment: Yes</td>
</tr>
<tr>
<td>Use in Renal Impairment: CrCl ≥ 30ml/min</td>
</tr>
<tr>
<td><strong>Paritaprevir/Ritonavir/Ombitasvir/ Dasabuvir (Viekira Pak®)</strong></td>
</tr>
<tr>
<td>Genotype: 1</td>
</tr>
<tr>
<td>Use in Hepatic Impairment: Mild</td>
</tr>
<tr>
<td>Use in Renal Impairment: Yes</td>
</tr>
</tbody>
</table>
Overview of Drug Interactions

Absorption Interactions

Cytochrome P450 & Transporter Mediated Interactions

Amiodarone

Immunosuppressant Interactions
Polling Question

• Which of the following drug-drug interactions are contraindicated in a solid organ transplant recipient being treated for HCV?

A. Glecaprevir/Pibrentasvir (Mavyret®) and pantoprazole 40mg PO daily
B. Ledipsavir/Sofosbuvir (Harvoni®) and omeprazole 20mg PO daily
C. Elbasvir/Grazoprevir (Zepatier®) and amiodarone 200mg PO daily
D. Velpatasvir/Sofosbuvir (Epclusa®) and amiodarone 400mg PO daily
Overview of Drug Interactions

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Cytochrome P450 & Transporter Mediated Interactions

Amiodarone

Immunosuppressant Interactions
# Effect of Food on DAA Absorption

<table>
<thead>
<tr>
<th>With Food</th>
<th>With or Without Food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glecaprevir/Pibrentasvir (Mavyret®)</td>
<td>Ledipasvir/Sofosbuvir (Harvoni®)</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir/ Voxilaprevir (Vosevi®)</td>
<td>Velpatasvir/Sofosbuvir (Epclusa®)</td>
</tr>
<tr>
<td>Paritaprevir/Ritonavir/Ombitasvir/ Dasabuvir</td>
<td>Elbasvir/Grazoprevir (Zepatier®)</td>
</tr>
<tr>
<td>(Viekira Pak®)</td>
<td></td>
</tr>
</tbody>
</table>
Effect of Gastric pH on DAA Absorption

• Some DAAs have gastric pH dependent absorption

• Stress-ulcer prophylaxis is commonly used after transplant

• Acid suppressants can negatively effect DAA absorption risking treatment failure
Clinical Effect of PPI Interaction

No PPI Use: 97.2%
PPI Use: 93.5%
Baseline PPI once daily: 94.3%
Baseline PPI twice daily: 80.6%

Gastroenterology 2016 Dec;151(6):1131-1140
Management of PPIs and DAAs

- Stop PPI
- Select another DAA
- Manage Interaction
Management of PPIs and DAAs

Ledipasvir

- PPI: Give together with ≤ 20mg omeprazole once daily on empty stomach
- With or 12 hours apart at dose that ≤ 40mg BID famotidine
- Antacids: separate by 4 hours

Velpatasvir

- PPI: ≤ 20mg omeprazole 4 hours after velpatasvir with food
- With or 12 hours apart at dose that ≤ 40mg BID famotidine
- Antacids: separate by 4 hours
Overview of Drug Interactions

Absorption Interactions

Cytochrome P450 & Transporter Mediated Interactions

Amiodarone

Immunosuppressant Interactions
<table>
<thead>
<tr>
<th>DAA Agent</th>
<th>Substrate</th>
<th>Inhibitor</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAA Agent</strong></td>
<td><strong>Substrate</strong></td>
<td><strong>Inhibitor</strong></td>
<td><strong>Other</strong></td>
</tr>
<tr>
<td></td>
<td>CYP3A4</td>
<td>P-gp</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Glecaprevir/ Pibrentasvir (Mavyret®)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Paritaprevir/ ritonavir/ Ombitasvir/ Dasabuvir (Viekira Pak®)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir (Zepatier®)</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Voxilaprevir</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

BCRP: breast cancer resistance protein; OATP: organic anion transporting polypeptide
Potential Drug Interactions

**Inducers**
- St John’s Wort
- Rifampin/ Rifabutin
- Carbamazepine
- Phenytoin
- Phenobarbital
- Efavirenz

**Inhibitors**
- Azole antifungals
- Protease Inhibitors
- Erythromycin/Clarithromycin
# Statins and DAAs

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin</th>
<th>Atorvastatin</th>
<th>Pitavastatin</th>
<th>Simvastatin</th>
<th>Pravastatin</th>
<th>Lovastatin</th>
<th>Fluvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>Max 10mg</td>
<td>NR</td>
<td>Use lowest dose</td>
<td>NR</td>
<td>↓ dose by 50%</td>
<td>NR</td>
<td>Use lowest dose</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>NR</td>
<td>Monitor closely</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Velpatasvir/Sofosbuvir</td>
<td>Max 10mg</td>
<td>Monitor closely</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>Max 10mg</td>
<td>Max 20mg</td>
<td>Use lowest dose</td>
<td>--</td>
<td>Use lowest dose</td>
<td>Use lowest dose</td>
<td>Use lowest dose</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir/Voxilaprevir</td>
<td>NR</td>
<td>Use lowest dose</td>
<td>NR</td>
<td>Use lowest dose</td>
<td>Max 40mg</td>
<td>Use lowest dose</td>
<td>Use lowest dose</td>
</tr>
<tr>
<td>Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir</td>
<td>Max 10mg</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Max 40mg</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

NR: not recommended, Per Package Labeling
Overview of Drug Interactions

Absorption Interactions

Cytochrome P450 & Transporter Mediated Interactions

Amiodarone

Immunosuppressant Interactions
Amiodarone-Sofosbuvir Induced Bradycardia

• Post-marketing reports of life-threatening bradycardia
• May occur within first few hours up to 2 weeks
• Exact mechanism unknown

https://www.fda.gov/Drugs/DrugSafety/ucm439484.htm
Management of Amiodarone and Sofosbuvir

• Avoid coadministration

• When discontinuing amiodarone prior to starting sofosbuvir, consider long half-life of amiodarone

• If coadministration is unavoidable
  – Counsel patients about risk of serious symptomatic bradycardia
  – Cardiac monitoring in an in-patient setting for first 48 hours of coadministration followed by daily heart rate monitoring

https://www.fda.gov/Drugs/DrugSafety/ucm439484.htm
Overview of Drug Interactions

Absorption Interactions

Cytochrome P450 & Transporter Mediated Interactions

Amiodarone

Immunosuppression Interactions
Cyclosporine and DAAs

- Cyclosporine is an inhibitor of CYP3A4 (weak), P-glycoprotein, OATP1B1, and BCRP
  
  **Glecaprevir/Pibrentasvir**
  - Use not recommended in patients requiring >100mg cyclosporine per day
  
  **Elbasvir/Grazoprevir**
  - Cyclosporine may increase risk of ALT elevations due to OATP inhibition

  **Sofosbuvir/Velpatasvir/Voxilaprevir**
  - Cyclosporine increases Voxilaprevir concentrations
  - Use not recommended
Calcineurin Inhibitor Dose Adjustments

<table>
<thead>
<tr>
<th>DAA Therapy</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>Dosing</td>
</tr>
<tr>
<td>Ritonavir-boosted</td>
<td>↑482%</td>
<td>1/5 total daily dose</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Hepatology 2016;63:634-643
https://www.hcvguidelines.org/unique-populations/post-liver-transplant
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D. Velpatasvir/Sofosbuvir (Epclusa®) and amiodarone 400mg PO daily
Common Adverse Effects

- Fatigue
- Headache
- Nausea
- Diarrhea
- Skin reactions (rare)
Overview Maintenance Immunosuppression

- Calcineurin Inhibitors
  - Tacrolimus
  - Cyclosporine

- Anti-metabolites
  - Mycophenolic acid
  - Azathioprine

- Corticosteroids
  - Prednisone

- mTOR Inhibitors
  - Sirolimus
  - Everolimus
# Cyclosporine vs Tacrolimus

<table>
<thead>
<tr>
<th></th>
<th>Levy et al.</th>
<th>Liu et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Prospective, randomized, open label, 356 liver txp recipients for HCV</td>
<td>Meta-analysis of 9 randomized and quasi-randomized controlled trials</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Tacrolimus vs Cyclosporine</td>
<td>Tacrolimus vs Cyclosporine</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Fibrosis ≥ stage 2 @ 12months FK vs CyA 67.5% vs 71.6% (P=0.759) HCV Viral Load @ 12 months FK vs CyA 3.13 U/μL vs 3.17 U/μL (P=0.866)</td>
<td>No difference found in: -mortality -graft loss -histological HCV recurrence</td>
</tr>
</tbody>
</table>

# Steroid Withdrawal

<table>
<thead>
<tr>
<th></th>
<th>Segev et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Meta-analysis of 30 publications (19 RCT)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Steroid-free vs Steroid-based</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>↓ HCV recurrence with steroid avoidance (RR 0.90, P=0.03)</td>
</tr>
</tbody>
</table>

## mTOR Inhibitors

<table>
<thead>
<tr>
<th>McKenna et al.</th>
<th>Soliman et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Single center, retrospective, 455 liver txp recipients with HCV</td>
</tr>
<tr>
<td></td>
<td>Single center, open-label, prospective, 25 renal txp recipients with HCV</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Sirolimus within 7 days of txp vs Non-sirolimus</td>
</tr>
<tr>
<td></td>
<td>Conversion to Sirolimus vs Cyclosporine</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Fibrosis on biopsy</td>
</tr>
<tr>
<td></td>
<td>HCV PCR @ 6 months:</td>
</tr>
<tr>
<td></td>
<td>SRL 700,000 → 400,000 IU/mL (P&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>CyA 680,000 → 660,000 IU/mL (P=NS)</td>
</tr>
</tbody>
</table>

1 year: 15.3% vs 36.2% (p<0.0001)  
2 year: 30.1% vs 50.5% (p=0.001)  

Patient Case Discussion

RH is a 54yo male with ICM now s/p OHT 6 weeks ago from a HCV positive donor. His post-op course was complicated by persistent afib. He presents to clinic for a routine cardiac biopsy and to see hepatology for initiation of hepatitis C therapy.

**PMH**  GERD, gout, and hypothyroidism

**Medications**
- Tacrolimus 3mg PO q12h
- Mycophenolate mofetil 1000mg PO q12h
- Prednisone 15mg PO daily
- Valganciclovir 450mg PO daily
- Nystatin Swish and swallow 5mL TID
- Bactrim DS qMWF

- Rosuvastatin 5mg PO qhs
- Aspirin 81mg PO daily
- Pantoprazole 40mg PO BID
- Levothyroxine 88mcg PO daily
- Allopurinol 300mg PO daily
- Amiodarone 200mg PO daily

**Pertinent Labs**
- Serum Cr: 2.1
- CrCl = 45ml/min
- LFTs: WNL
- TFTs: WNL
- Hepatitis C PCR: 2 million
- HCV Genotype: 1
RH is a 54yo male with ICM now s/p OHT 6 weeks ago from a HCV positive donor. His post-op course was complicated by persistent afib. He presents to clinic for a routine cardiac biopsy and to see hepatology for initiation of hepatitis C therapy.

- What are some patient-specific issues to consider in selecting his hepatitis C therapy?
- Which DAA would you select? Are there any changes you would recommend to his other medication therapy?
Challenges of Hepatitis C Therapy After Transplant

• Compliance with Complicated Medication Regimens

• Complex Drug Interactions involving DAAs and transplant medications

• Side Effect Management

• Cost
Key Takeaways

- There are a variety of drug interactions with DAAs that require careful consideration of patient-specific factors, especially after solid organ transplant.

- In the current era of DAAs, standard immunosuppression should be used post-transplant for patients receiving hepatitis C positive donors.
Acknowledgements

• ASHP Section of Clinical Specialists and Scientists

• American Society of Transplantation Transplant Pharmacist Community of Practice Education Workgroup