TREATMENT OF HCV IN KIDNEY TRANSPLANT RECIPIENTS

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DISCLOSURES

• No conflict of interest
Lecture Outlines

Candidates - HCV patients eligibility for kidney transplant

Transplant - Timing of kidney transplant and antiviral treatment for HCV patients

Recipients - Choice of immunosuppression for transplant recipients

Donors - HCV kidney donor
Hepatitis C infection

Kidney Transplant Eligibility
SHOULD KIDNEY TRANSPLANT BE OFFERED?

• Are HCV patients having worse outcome after kidney transplant?

• Should HCV status affect the eligibility of kidney failure patients for kidney transplant waiting list?
HCV AND KIDNEY TRANSPLANT OUTCOMES

- Organ Procurement and Transplantation Network database
- 33,357 adult primary kidney transplant recipients, 1470 (4.4%) were HCV-positive
- 1364 HCV-positive and -negative pairs selected by propensity score matching

Worse Transplant Outcomes

When HCV-positive and -negative kidney transplant recipients were carefully matched, HCV was associated with:

• Lower long-term recipient survival (attributable to infection and liver failure)
• Lower long-term death-censored graft survival

(similar for deceased donor and live donor recipients)

COMPARE TRANSPLANT WITH DIALYSIS

What about survival of HCV patients on dialysis and that after kidney transplant?

Recent US analysis of 442,171 dialysis patients (7.2% HCV seropositive) from 2004 to 2014

SURVIVAL BENEFIT OF TRANSPLANT OUTCOMES

Less likelihood of entry to transplant waitlist (HR, 0.67; 95% CI, 0.61-0.74)

And yet ...

HCV-seropositive patients lived longer with transplantation (aHR at 3 years, 0.42; 95% CI, 0.27-0.63) compared to remaining on the waitlist

SURVIVAL BENEFIT OF TRANSPLANT OUTCOMES

Hazard ratio for death

kidney transplantation compared to remaining on the waiting list

KDIGO Recommendation

4.1.1: We recommend kidney transplantation as the best therapeutic option for patients with CKD G5, irrespective of presence of HCV infection (1A).
Hepatitis C treatment

Kidney transplant
2008 KDIGO guidelines:

• Treat HCV in patients waitlisted for transplant to eradicate infection while on dialysis
• But IFN-based therapy is poorly tolerated

Transplant Recipients

- Interferon IFN linked to acute graft rejection (even with nonfunctioning grafts)
- Not recommended for kidney transplant recipients by 2008 KDIGO guidelines (unless pressing indications such as clinically and histologically worsening liver disease)
- Ribavirin also causes anaemia by provoking haemolysis

IFN AND REJECTION RISK

• Meta-analysis of 12 studies covering 140 kidney transplant recipients
• 21% dropout due to side effects (graft dysfunction the most frequent reason)
• Rejection rate: 10 out of 140 treated patients
CHANGING LANDSCAPE
Nothing is permanent. Everything CHANGES. That's the one thing we know for sure in this WORLD.

Calvin and Hobbes Wisdom Quotes via Gecko&Fly
Identification of a ‘non-A non-B’ hepatitis

Identification of HCV

The DAA revolution

Pan-genomic era


IFN IFN and RBV Peg-IFN and RBV

The IFN era (with PEG-IFN)

Early era of DAAs

TVR SMV DCV LDV/SOF EBR/GZR G/P

SOF/VEL SOF/VEL/VOX

OBV/PTV/r and DSV

NS5 inhibitors Polymerase inhibitors Protease inhibitors

HCV elimination?

KDIGO Recommendation

4.1.3:
We recommend that all HCV-infected patients who are candidates for kidney transplantation be considered for DAA therapy, either before or after transplantation (1A).
DAA: CHANGE THE SCENE

Can wait until after kidney transplantation
**TRANSPLANT CANDIDATES**

Factors to consider (for timing of HCV treatment):

• severity of liver disease or extrahepatic manifestations
• eligibility for antiviral regimens with established safety in severe renal impairment
• estimated waiting time on the renal transplant list
BEFORE OR AFTER TRANSPLANT?

**Treating before transplant**
- Effective pan-genotypic regimens
- Halts progression of liver disease
- Decreases dialysis transmission
- Decreases de novo GN after transplant
- Reduces NODAT risk
- May improve extrahepatic manifestations

**Treating after transplant**
- Effective pan-genotypic regimens
- Does not increase the risk of rejection
- Decreases transplant wait time
- Increases organ utilization
- Reduces overall cost burden

HOW LONG TO WAIT AFTER TRANSPLANT

• Case-by-case decision

• Don’t want to wait for too long, or post-transplant complication will ensue

• Don’t want to treat too early (first 6 months), when CNI dosage needs adjustment (drug interaction)
<table>
<thead>
<tr>
<th>Antiviral agents</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>$\uparrow$ CsA and SMV levels</td>
<td>Monitor TAC levels</td>
<td>Monitor SRL levels</td>
<td>Monitor EVL levels</td>
</tr>
<tr>
<td>Ombitasvir, Paritaprevir, ritonavir, Dasabuvir</td>
<td>$\uparrow$ CsA levels</td>
<td>$\uparrow$ TAC levels</td>
<td>Monitor SRL levels</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
<td>Monitor EVL levels</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
<td>Monitor SRL levels</td>
<td>Monitor EVL levels</td>
</tr>
<tr>
<td>Elbasvir, Grazoprevir</td>
<td>$\uparrow$ GZV levels</td>
<td>$\uparrow$ TAC levels</td>
<td>Monitor SRL levels</td>
<td>Monitor EVL levels</td>
</tr>
<tr>
<td>Glecaprevir, Pibrentasvir</td>
<td>$\uparrow$ G/P levels</td>
<td>$\uparrow$ TAC levels</td>
<td>Monitor SRL levels</td>
<td>Monitor EVL levels</td>
</tr>
</tbody>
</table>

- **Calcineurin Inhibitors**:
  - Cyclosporine:
    - Monitor TAC levels
  - Tacrolimus:
    - Adjust TAC dose

- **Mammalian target of rapamycin inhibitors**:
  - Sirolimus:
    - Monitor SRL levels
  - Everolimus:
    - Monitor EVL levels

- **Adjustments**:
  - Not recommended
  - Monitor TAC levels
  - Adjust CsA dose
  - Adjust TAC dose

- **Note**: KDIGO
CONSULT THE WEBSITE

• Hepatitis Drug Interactions website from the University of Liverpool
  - http://www.hep-druginteractions.org

• Check for the latest guidance on potential drug–drug interactions prior to DAA use
<table>
<thead>
<tr>
<th>Pros</th>
<th>Pre-transplant HCV treatment</th>
<th>Post-transplant HCV treatment</th>
</tr>
</thead>
</table>
| Pros | • Limit risk of progressive liver injury in pre-transplant period  
     • Avoid risk of progressive HCV liver disease and fibrosing cholestatic hepatitis following transplant  
     • Provides optimum use and timing of a live donor graft | • Accept HCV-positive donors  
     • Shorter wait-list time  
     • Increase kidney donor pool |
| Cons | • Potentially preclude use of HCV-positive organs  
     • Longer wait-list time and risk of death on dialysis | • Still at risk of progressive liver disease  
     • Still at risk of hepatocellular carcinoma  
     • Longer wait for treatment of HCV post-transplant may leave them at risk of diabetes, graft failure, decreased survival |
Hepatitis C treatment
Kidney transplant
Immunosuppression
WHAT IMMUNOSUPPRESSION TO USE

• Concerns of increase in HCV viral load after transplantation

• Any caution with impact of induction and high dose maintenance immunosuppression?
• Any concern with transplant survival?

• Antibody induction has not been linked to worse survival in HCV-positive patients with post-transplantation chronic liver disease

• Limited data on influence of steroids in kidney transplant patients with HCV infection, but no difference in mortality in a US study
HCV AND METABOLIC COMPLICATIONS

• Increased insulin resistance after chronic HCV infection

• Meta-analysis (> 30,000 kidney transplant recipients): relative risk of post-transplant diabetes mellitus is 2.73-fold higher

• Can the risk be modified by immunosuppression?

• No significant difference in outcomes with cyclosporines versus tacrolimus in HCV-infected transplant recipients
• Higher risk of post-transplant diabetes mellitus in tacrolimus-treated patients

Cox regression model of NODAT / PTDM

Risk of NODAT (first posttransplant year)

Adult transplant recipients (n = 97 644)

Hazard Ratio

Reference for All Comparisons: Tac+MPA

Hepatitis C antibody - Hepatitis C antibody + CMV antibody - CMV antibody +

Other risk factors: ATG: HR=0.92, CI=0.98-0.86; Abcam: HR=0.62, CI=0.69-0.66; Other induction: HR=0.9, CI=0.99-0.81; Transplant Year '05-'15: HR=2.2, CI=2.42-2.8; Deceased Donor: HR=1.11, CI=1.18-1.05; Recipient Age 45-60 yr.: HR=1.87, CI=2.0-1.76; Recipient Age >60 yr.: HR=2.12, CI=2.28-1.98; Black Race: HR=1.47, CI=1.57-1.38; Hispanic Race: HR=1.2, CI=1.3-1.1; Other Race: HR=1.51, CI=1.67-1.36; BMI 25-29: HR=1.46, CI=1.58-1.36; BMI >30: HR=2.17, CI=2.32-2.03; BMI unknown: HR=1.77, CI=1.95-1.6; steroids: HR=0.99, CI=1.15-0.95

CONVERSION OF FK TO CYCLOSPORIN

- Single-center study: 10 HCV-positive renal transplant recipients with OGTT before and three months after the conversion
- Significantly improved glucose-stimulated insulin sensitivity and overall glucose tolerance

• Cyclosporine inhibits HCV replication on cultured hepatocytes

OTHER IMMUNOSUPPRESSION

• Change to MMF (n = 14): increased serum HCV RNA from 5.2 ± 0.7 to 5.8 ± 0.5 log copies/ml (P=0.01)

• Data on sirolimus and everolimus: limited in patients with HCV infection
KDIGO Recommendation

4.3.1:
We suggest that all conventional current induction and maintenance immunosuppressive regimens can be used in HCV-infected kidney transplant recipients (2C).
Hepatitis C Kidney Donor
Can transplant HCV-positive kidneys into HCV-negative recipients?
THINKER TRIAL

- Transplanting Hepatitis C Kidneys into Negative Kidney Recipients
- Kidneys from HCV genotype 1–viraemic donors into 10 HCV-negative patients
- Recipients monitored for HCV viraemia starting at postoperative day 3
- Once HCV RNA detected: elbasvir–grazoprevir (Zepatier) treatment for 12 weeks

THINKER TRIAL

• Donor-to-recipient HCV transmission: 100%

• Two cases of elevated ALT

• All recipients were cured of HCV (sustained virologic response SVR12)

THINKER TRIAL – 12 MONTH RESULT

• First 10 recipients – 12 month data (THINKER-1)
• Additional 10 recipients – 6 month data (THINKER-2)

• Primary outcome – all achieved cure of HCV

THINKER TRIAL – 12 MONTH RESULT

- Mean Physical Component Summary (PCS) and Mental Component Summary (MCS) quality-of-life scores decreased at 4 weeks
- PCS scores then increased above pretransplant values
- MCS scores returned to baseline values

### Table 2. Comparison of eGFRs and Creatinine Levels at 6 and 12 Months Between THINKER Participants and Matched Comparator Recipients of Kidneys From HCV-Negative Donors

<table>
<thead>
<tr>
<th>Variable</th>
<th>THINKER Recipients (n = 10 or 20)*</th>
<th>Matched Allocation KDPI Comparators (n = 50 or 100)*</th>
<th>Matched Optimal KDPI Comparators (n = 50 or 100)†</th>
<th>Difference Between Matched Sets of THINKER Recipients and Allocation Comparators (95% CI)‡</th>
<th>P Value for Comparison With Allocation Comparators‡</th>
<th>P Value for Comparison With Optimal Comparators‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6-mo outcomes</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Creatinine level</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>μmol/L</td>
<td>103 (90 to 118)</td>
<td>117 (95 to 150)</td>
<td>106 (88 to 124)</td>
<td>−20 (−29 to −11)</td>
<td>&lt;0.001</td>
<td>0.37</td>
</tr>
<tr>
<td>mg/dL</td>
<td>1.2 (1.0 to 1.3)</td>
<td>1.3 (1.1 to 1.7)</td>
<td>1.2 (1.0 to 1.4)</td>
<td>−0.2 (−0.3 to −0.1)</td>
<td>−4 (−11 to 4)</td>
<td>0.04 (−0.1 to 0.1)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>67.5 (57.8 to 85.7)</td>
<td>56.6 (48.3 to 74.6)</td>
<td>66.2 (55.3 to 81.9)</td>
<td>10.5 (4.8 to 16.2)</td>
<td>&lt;0.001</td>
<td>1.6 (−4.2 to 7.5)</td>
</tr>
<tr>
<td><strong>12-mo outcomes</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Creatinine level</td>
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<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.33</td>
</tr>
<tr>
<td>μmol/L</td>
<td>98 (84 to 111)</td>
<td>106 (95 to 141)</td>
<td>97 (80 to 115)</td>
<td>−21 (−31 to −12)</td>
<td>−4 (−12 to 4)</td>
<td>0.04 (−0.1 to 0.1)</td>
</tr>
<tr>
<td>mg/dL</td>
<td>1.1 (1.0 to 1.3)</td>
<td>1.2 (1.1 to 1.6)</td>
<td>1.1 (0.9 to 1.3)</td>
<td>−0.2 (−0.4 to −0.1)</td>
<td>−0.04 (−0.1 to 0.1)</td>
<td></td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>72.8 (58.6 to 74.4)</td>
<td>57.7 (46.0 to 68.6)</td>
<td>67.2 (55.8 to 78.3)</td>
<td>13.6 (7.9 to 19.2)</td>
<td>&lt;0.001</td>
<td>1.4 (−7.2 to 9.8)</td>
</tr>
<tr>
<td>Delayed graft function, n (%)</td>
<td>5 (25)</td>
<td>45 (45)</td>
<td>32 (32)</td>
<td>NA</td>
<td>0.076</td>
<td>NA</td>
</tr>
</tbody>
</table>

eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; IQR = interquartile range; KDPI = kidney donor profile index; NA = not applicable; THINKER = Transplanting Hepatitis C kidneys Into Negative Kidney Recipients.

* As expected, 20 THINKER recipients had creatinine and eGFR values at 6-mo follow-up and 10 THINKER recipients had creatinine and eGFR values at 1-y follow-up. Each THINKER recipient was matched to 5 comparators.

† This group comprised recipients of kidneys with KDPI scores that were recalculated as if donors were HCV-seronegative.

‡ For between-group comparisons of creatinine level and eGFR, the comparator value was subtracted from the THINKER value. The differences, CIs, and P values were calculated using in-statistics (see the Methods section in Supplement 1 [available at Annals.org]), which account for small numbers of THINKER recipients and the 1:5 matching. For between-group comparisons of delayed graft function, the P values were calculated using conditional logistic regression.

Further Expansion of Donor Pool

• EXPANDER

• Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV Negative Recipients

EXPANDER: IMPLICATIONS OF STUDY DESIGN

• Allow organ from HCV infected donors with any HCV genotype
• Not require virologic or genotypic assay at the time of organ offer and allocation

EXPANDER

- Industry-funded pilot study in John Hopkins University
- 10 HCV D+/R− kidney transplant candidates without living donors
- Deceased donors aged 13 to 50 years with positive HCV RNA and HCV antibody test
- Testing tolerability and feasibility of prophylactic DAA for recipients

RECIPIENTS WITH HCV-INFECTED DONORS

• Median wait time 1 month
• GPZ-EBR regime: Grazoprevir and elbasvir immediately before surgery and daily for 12 weeks after surgery
• Donors with genotype 2 or 3 HCV: additional sofosbuvir (GPZ-EBR + SOF) after transplant

OUTCOMES OF HCV D+/R- KIDNEY TRANSPLANT

• 12 weeks' follow-up
• No treatment-related adverse events
• No recipient became infected with chronic HCV
• Over half of recipients had HCV RNA levels below the lower limit of quantification (LLOQ)

HCV RNA TREND IN TRANSPLANT RECIPIENTS

CONCLUSION

HCV IN KIDNEY TRANSPLANT
CONCLUSION

- Kidney transplantation is the best therapeutic option for patients with CKD G5, irrespective of presence of HCV infection.
- All HCV-infected patients who are candidates for kidney transplantation to be considered for DAA therapy, either before or after transplantation.
- All conventional current induction and maintenance immunosuppressive regimens can be used in HCV-infected kidney transplant recipients.
Candidates waiting for transplant

Transplant recipients

HCV kidney donors