HCV in the era of Direct Acting Antiviral (DAA) Therapy

Impact on transplant candidates and recipients

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Objectives

- Discuss the goals of DAA therapy in waitlisted patients with HCV decompensated cirrhosis and the challenges regarding appropriate timing of treatment.
- Explore how DAAs offer the opportunity to expand the organ donor pool.
- Review the guidance from International Societies regarding HCV positive grafts for HCV +/− recipients
- Discuss future research challenges to study the use of DAAs at various time points during the transplant continuum in patients with highest clinical need for organ transplantation

Disclosure

I have no relevant financial relationships with any companies related to the content of this course.

Reduction in Liver transplant wait-listing in era of DAAs

Flemming et al. Hepatology 2017(65)
Clinical cases: which transplant candidate would you treat now?

Patient A: 59 year old woman with HCV GT 3 decompensated cirrhosis (CPT B) with ascites, blood type O, MELD 15

Patient B: 59 year old woman with HCV GT 3 decompensated cirrhosis (CPT B) with ascites, blood type O with HCC exception points MELD 28

Patient C: 62 year old man with HCV GT 1 decompensated cirrhosis and HRS, listed for combined liver/kidney blood type AB, MELD 29

HCV treatment in liver transplant candidates should be individualized

Key question: will patient achieve clinical benefit from HCV eradication?

Treatment goals for decompensated patients with HCV:
1. Stabilize liver disease, improve QOL, promote delisting
2. Prevent HCV recurrence post transplant
3. Prevent waitlist drop off due to worsening decompensation

Treat selectively and individualized, considering:
- Anticipated time to transplantation
- Access to living donor LT

What are treatment options for patients with Decompensated Cirrhosis?

Case A: HCV GT3 woman with decompensated cirrhosis (CPB) with ascites, MELD 15

- Sofosbuvir-Ledipasvir + RBV for 12 weeks GT 1-4
- Sofosbuvir-Velpatasvir + RBV for 12 weeks GT 1-6
- NS5a failure: Sofosbuvir-Velpatasvir + RBV for 24 weeks OR Ledipasvir-Sofosbuvir + RBV for 24 weeks (GT 1, 4, 5, 6 only)

RBV ineligible
- Sofosbuvir-Velpatasvir x 24 weeks
- Sofosbuvir-Ledipasvir x 24 weeks (GT 1, 4, 5, 6 only)

AASLD-IDSA Hepatitis C Guidance, HCVguidelines.org. Accessed August 31, 2018
Charlot M. N Engl J Med. 2015;373:2618-28
Which patients may be able to avoid liver transplant?

Patients with a baseline MELD <16 have a 50% chance of delisting
Patients with a baseline MELD >20 with only 15% chance of delisting

DAA therapy has led to clinical benefit in select liver transplant candidates

European (ELTR/ELITA) registry study > 60,000 pts
- 50% reduction in liver transplants for HCV decompensated cirrhosis after DAAs
- 30% of decompensated cirrhosis with MELD < 20 delisted due to clinical improvement after HCV clearance from DAAs

UCSF CP B/C Cohort: 204 CP B/C pts without HCC who achieved SVR:
- 26% of CP B/C patients re-compensated
- 36% still decompensated → “MELD Purgatory”
- 17% deaths, 13% transplanted
- Patients with more severe portal HTN at BL were more likely to end up in MELD purgatory

Is There a “Point of No Return” for Patients with Decompensated Cirrhosis?

Almost certainly yes.....
Primary reasons:
- Insufficient time to improve (before worsening decompensation, HCC or death)
- Inability to regenerate, repair and reverse

Impact of SVR on waitlist mortality and liver transplant

Achieving SVR is associated with lower likelihood of death and transplantation
Baseline predictors associated with improvements after SVR in CP B/C cirrhosis

**BE3A score - baseline factors:**

<table>
<thead>
<tr>
<th>Category</th>
<th>Findings</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt; 25 kg/m²</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>ALT &gt; 1.5xULN</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Albumin &lt; 3.5g/dL</td>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

Future challenge: Defining Who on the Waiting List Should NOT be Treated

Consider **pre-treatment predictors** when trying to determine whether or not to treat decompensated patients
- MELD, severity of PHT complications, BE3A score

There are clues from available data but additional markers needed...
- More studies need to capture delisting, MELD purgatory AND wait-list mortality if untreated

Clinical scenario, patient B

Patient B: 59 year old woman with HCV GT3 decompensated cirrhosis (CPB) with ascites, Blood type O, with HCC exception points MELD 28.
- Ascites is refractory to diuretics
- HCC still within Milan and likely has > 6-12 month wait to LT.
- You discuss options living donation but she has no living donor.

You recommend deferring DAA therapy, and consent for high risk donor option to receive liver from donor with HCV

Timing of DAAAs in patients listed for liver transplant

MELD STATUS

- < 20
- ≥ 20
- ≥ 3-6 mo
- ≥ 6 mo

Cirrhosis

DAA

LT

DAA (post-LT)

HCC + Cirrhosis

Priority of LT

DAA

LT

DAA (post-LT)
Deferring treatment after organ transplant

Patient C: 62 year old man with HCV GT 1 decompensated cirrhosis and HRS, listed for combined liver/kidney Blood type AB, MELD 28

- His HRS has progressed to CKD and he is now on HD
- Note: No currently no FDA approved treatment option for a decompensated patient with CrCl < 30ml/min.

You recommend deferring DAA therapy, and consent for high risk donor option to receive liver/kidney from donor with HCV.

Use of HCV + donors in organ transplantation is changing

Proportion of patients who received HCV+
LT increased by 10% from 2010 to 2015
Discard rate declined from 28% to 11%

Levitsky et al. American J of Transplantation 2017. 17; 2790-2802;
Bushyhead and Goldberg. Current Hepatol Reports 2017 16(1) 12-17

Median age of donors has decreased from 47 y.o. to 35 y.o

Guidance from International Societies

Anti-HCV seropositive donor → HCV viremic recipient

AST: The use of HCV+ donors in HCV viremic recipients is acceptable in routine clinical practice

LTST: Recommends the use of HCV+ grafts in HCV viremic recipients

Caveats:
- Anti HCV positive donors should be restricted to patients with high clinical need.
- Quality of graft should be carefully evaluated—younger donors, < F2 fibrosis.
- Since 2014, OPTN recommends HCV NAT testing, but if results not available, consider organ to be HCV viremic.

Guidance from International Societies

HCV seropositive donor → HCV PCR negative recipient

AST: “DAA therapy makes the expansion of transplanting HCV seropositive donors into non-viremic recipients a possibility and can save lives. Urgent need exists for prospective research protocols that study the risk versus benefit of using organs from HCV infected donors.”

Suggest a limited use of anti-HCV positive grafts in anti-HCV or HCV RNA negative recipients. IRB approval needed to discuss risks with informed consent and recommend very early DAA therapy.

Terrault et al. Transplantation. 2017;101(5);
Effective Use of Antivirals Can Prevent Graft Loss

Multiple potential time-points to intervene

- Prevent infection or hepatitis
- Prevent cirrhosis and graft failure

DAA therapy and Impact on Survival of Transplant recipients

European Liver Transplant Registry:
- Since 2014, The 3-year post LT transplant survival has increased from 65% to 76% (comparable to post transplant pts with HBV)
- In the IFN era, post-transplant treatment was deferred until evidence of significant fibrosis (F2 or higher) or severe cholestatic recurrence
- Now, guidelines recommend treating earlier post-LT as earlier treatment is possible with DAA therapy
  - Typically within first 3 months – ILTS
  - 3-6 months post-LT – ELTS
  - When patient is “clinically stable” and with stable IMS

Pan genotypic regimens in post organ transplant recipients

Glecaprevir/pibrentasvir for 12 weeks for transplant recipients

- Sustained Viologic Response: 96%
- 80 liver transplant recipients
- 20 kidney transplant recipients
- Mostly low stage fibrosis, no pts had cirrhosis
- Mostly on tacrolimus for IMS

Pangenotypic regimen post liver transplant recipients

Sofosbuvir/velpatasvir for 12 weeks for transplant recipients

- SVR12: 96, 95, 93, 96, 100, 97, 100, 100, 94, 100, 95
- 3 patients did not achieve SVR: one early D/C and 2 relapses
- 4/4 patients with baseline Y93H RASs (3 GT 3 and 1 GT 1b) achieved SVR12
- No changes in immunosuppression were needed for rejection or suspected drug-drug interactions

- DDI: PPI use discouraged, prefer D/C PPI or substitute with H2 blocker
SOF/LDV still an option for GT 1,4-6 post transplant recipients—HCV TARGET Real World Experience

Factors Predictive of SVR

Although AASLD recommends + RBV, may consider SOF/LDV alone for early fibrosis

What About Preemptive HCV Therapy for liver transplant recipients?

Preemptive Therapy for HCV Liver Transplant Recipients

- Potential advantages of preemptive therapy
  - likely most cost-effective strategy
  - UCSF protocol for HCV D-R+ → SOF/VEL x 4 weeks “CRUSH”
  - UCSF protocol for HCV D+R+ → SOF/VEL x 12 weeks

- Caveats:
  - Need CrCl >30 ml/min to use a SOF-based regimen
  - Centers are currently studying HCV + donor

- What do the guidelines say?
  - Should be used selectively – ILTS
  - Not recommended on routine basis, consider early DAA treatment before biochemical manifestations - ELITA

Risk of Rejection in Context of HCV Therapy

- Interferon was associated with allograft complications
  - AR/CR
  - Plasma cell (or alloimmune) hepatitis
  - DAA therapy not directly associated with these risks
  - Decline in IMS levels in association with viral clearance reported → risk of rejection if IMS doses not adjusted
  - Immunologic graft dysfunction (IGD) after DAAs occurred in 3.4% (median time 76 days post DAA) in multicenter study

SUMMARY

- DAAs are changing the landscape of organ transplantation and should be used selectively in decompensated waitlisted patients.
- More research needed to capture data on delisting, MELD purgatory and waitlist mortality for treated/untreated patients with decompensated cirrhosis.
- HCV positive grafts for HCV viremic patients is recommended and pre-emptive pan-genotypic DAA therapy offers an opportunity for significant cost savings.
- Use of HCV seropositive grafts for non-viremic recipients is currently being entertained in the setting of prospective research protocols with very early pan-genotypic DAA therapy.
- Although post-transplant pan-genotypic DAA therapy has become simplified without need for RBV in most patients, it still requires close monitoring of IMS levels and laboratory work to rule out rejection/IGD.