Liver Transplantation Utilizing Donor Livers From HCV RNA Positive Donors Into HCV RNA Negative Recipients

Diane Alonso MD, FACS
Surgical Program Director Abdominal Transplant, Intermountain Medical Center
Medical Director, Intermountain Donor Services
Salt Lake City, UT

Diane Alonso MD, Shiro Fujita MD PhD, Ivan Zendejas MD, Manuel Rodriguez MD, Gordon Harmston MD, Robert Jones MD, Edward Frech MD, Mark Boschert MD, Lance Lindbergh PharmD, Michael Charlton MD, Richard Gilroy MD

Region 5 Collaborative Meeting
January 31, 2018
I have no relevant financial relationships to disclose.

(M. Charlton – Gilead, AbbVie, Merck, Janssen, Bristol-Myers-Squibb; Consulting/Research)
Setting The Stage...
Median MELD scores for adult deceased donor liver transplant recipients by DSA, 2015
Differences in lab MELD and allocation MELD scores among liver transplant recipients by DSA, 2015
• Competing risks
  • ~40% pts are removed from the IMC waitlist; many due to severe increase in frailty from progression of disease, malignant disease progression, relisting at another center outside our region, etc while awaiting transplant
    o High regional MELD (average 38) required for a pt to gain access to transplant in Region 5
    o IMC average MELD in 2015 – 37 for blood type O, 32 for blood type A
Setting the Stage: Continued

- Release of Direct Antiviral Therapy for HCV – 2014
- Proven Efficacy Post-OLT – end of 2015
- February 2016 – HCV D+/R- transplantation proposed
- First HCV D+/R- liver transplant - September 2016
The Big Question

Can We Get The Treatment Paid For?
The Unknowns

- Optimal timing for initiation and duration of treatment post-OLT
- Limitation of Direct Acting Antivirals (DAAs) – G2&3?
- Possible long term extra- or intra-hepatic complications and/or treatment failures
- Risk of malignant transmission from an HCV D+ graft
- Assessing degree of fibrosis in the graft with acceptable reliability
Initial HCV RNA Positive Donor Inclusion Criteria

- Brain Dead Donor
- Age $\leq 45$ yrs (to minimize risk of HCC and/or significant fibrosis)
- Normal bilirubin
- No h/o laboratory or clinical evidence of portal hypertension
- HBcAb + status acceptable
- Negative nucleotide testing for HBV
Initial HCV RNA Positive Donor Inclusion Criteria

- No radiographic evidence of cirrhosis or portal HTN
- No evidence of abnormal fibrosis on donor liver biopsy
- Normal macroscopic appearance and feel of graft at recovery
HCV RNA Positive Donor Acceptance Criteria

**All HCV RNA + donors require 2 physician review for acceptance or decline**

- Both physicians must personally review the following:
  - CT scan images – report not sufficient
  - Liver biopsy slides – images or actual slides required, report not sufficient
  - Intra-procurement photos of graft
  - If available at procurement, Fibroscan measurements
Burden of UTLD Pre-Recovery Requests on Hosting OPOs

- Uploaded CT scan images
- Uploaded, texted, or emailed images of biopsy slides
- Pre-Recovery biopsy or Intra-Op Biopsy
  - Pre-Recovery biopsies required to be able to entertain East coast recoveries due to pilot time constraints on the ground
- OPO willingness to be flexible setting Donor OR times
  - Particularly with East Coast OPOs
  - Long flight times and arranging coastal flights/charters can take up 10-12 hours
Initial Protocol Recipient Criteria

- HCV Ab/RNA negative status
- Patients must have one or more of the following:
  - life threatening conditions
  - recurrent hospitalizations
  - clinically sicker than their MELD and impacting quality of life
  - diagnosis of HCC or CCA
Initial Protocol Recipient Criteria

- Prior to listing the candidate must have undergone HCV+ donor specific verbal education by a physician (surgeon or hepatologist)
  - EMR documentation of discussion
- Pre-listing written consent also obtained
- Second verbal and written consent obtained by surgeon on admission for transplant
  - EMR documentation by surgeon of verbal consent discussion
- Absence of prior failure of DAA (direct acting antiviral) therapies
- Lack of pre-determined ability to pay for anticipated DAA therapy post-LT is a contraindication to receiving a HCV+ graft.
Intermountain Medical Center HCV Treatment Protocol Algorithm

- **Obtain HCV RNA Quant with reflex Genotype on POD 4**
- **Obtain HCV RA NQuant with Reflex Genotype on POD 7, 30, and 90**

- **HCV Donor NAT + Transplant**
  - HCV Recipient -
  - HCV Recipient +

- **Evidence of cholestatic liver disease**
- **Begin treatment based on genotype on POD 90**

**HCV Recipient -**
- **Discuss treatment with Liver Transplant Medical Director**
- **Submit prescription to insurance for prior authorization. Treatment based on HCV Treatment Grid**
- **Rx will commence as soon as approval obtained and pt clinically appropriate for tx**
  (w goal to start tx within 4 weeks of OLT for D+/R- pts)

**HCV Recipient +**
- **Begin treatment based on genotype on POD 90**

**Once approved all patients will present to clinic for education and review of medications by Transplant Pharmacist**
- **IMC Specialty Pharmacy will ensure medication provision**
- **Order Labs based on HCV Treatment Lab Protocol in iCentra**
- **Review in clinic at week 4 and 12 of therapy with APC or physician**
- **Review of labs at 12 weeks post treatment to assess SVR**
- **In those approved and on treatment, should they be admitted their outpatient prescription will be continued as an inpatient and overseen by transplant pharmacy**
Originating Donor OPO

12 Organs
9 National Offers
3 Regional Offers
HCV RNA + Donor Stats

- Average Donor Age – 31
  - Average DSA Import Donor Age 49
  - Average DSA Export Donor Age 34
- 80% of donors were Male
- 92% PHS increased risk
  - In comparison to our observed rate of 29% in our recipients of non HCV donors
- 34% HBcAb+
HCV RNA + Donor Stats

- Median CIT 7.34 hrs (5 hrs 37 min – 9 hrs 52 min)
  - Average CIT 6.25 hr for non-HCV group
- LFTS – terminal median tbili 0.6/AST 39/ALT 70/INR 1.2
  - One graft with terminal tbili of 7.6
- 100% with pre-recovery/intra-op liver biopsy and CT scans
  - All biopsies slides visually reviewed by 2 transplant physicians (surgeon/hepatology)
  - All with none - up to stage 2 fibrosis (with some later liberation on inclusion criteria)
  - All with <5% macrosteatosis
    - excluding one graft - 50% macro, 40% micro
HCV D+ Recipient Stats

- Most common indications for transplant were NASH (7) and PSC (5)
  - Average age – 49.1 y
- Median Days Listed - 602
  - Range 282-5632 days
- Median Lab MELD 28/ Allocation MELD 29
  - Regional average MELD 38 ( IMC average MELD 35)
- UNET sequences ranged from 1-95
- Median LOS after transplant – 8.25 d
HCV D+/R- Post- OLT Genotype

Number of Patients

- 1A/1B: 5
- 3A: 6
- 2: 1
Post-OLT Treatment Outcomes To Date

- 6/12 recipients have completed treatment* and achieved SVR
  - G1A/B – 5 pts
    - 4 pts rx’d with Sofosbuvir/Ledipasvir x 12wks
    - 1 pt rx’d with Sofosbuvir/Velpatasvir x 12wks
  - G3A – 1 pt
    - Sofosbuvir/Ledipasvir x 12wks

* Current Rx Protocol recently changed to pangenotypic therapy (Glecaprevir/Pibrentasvir) x 8 wks for all genotypes

**Immunosuppression: Induction – Steroids/Basiliximab 20 mg IV POD0/4; Maintenance- CNI (FK)/MMF/steroids
Post-OLT Treatment Outcomes To Date (Continued)

- 1/12 currently on therapy
  - G3A – Sofosbuvir/Ledipasvir x 12 wks
- 3/12 awaiting initiation of therapy
  - all G3A and approved for Sofosbuvir/Ledipasvir
- 1 patient had initiation of treatment held once they were diagnosed with peritoneal mesothelioma post-OLT
  - G2 but approved for Sofosbuvir/Ledipasvir after resubmission for approval
- 1 patient transplanted for PSC/CCA died from a ruptured bilio-hepatic artery fistula prior to completion of therapy
  - G3A – approved for Sofosbuvir/Ledipasvir after resubmission for approval prior to death
Post-OLT Graft Function

- 1/12 patients diagnosed with mild ACR
  - Treated with increase in CNI, Rx delayed until resolved

- All patients with excellent graft function to date
  - Average tbili 0.5/AST 24/ALT 23 (for pts that have completed Rx)
  - 1 pt dx’d w recurrent HCV (based on biopsy) prior to Rx authorization, Rx initiated and recurrence treated
  - No occurrences of post transplant cholestatic HCV
Impact On Staff/Process

- Significant increase in call burden
- 2 physician discussion with biopsy slide and CT reviews
- Surgeon phone consent
- Increase in travel frequency
  - DSA – 51% w avg flight time of 1.2-2 hrs
    - Cost ~ $15,000
  - HCV D+/R- donor group - 100% w flight times 3-4.5 hours one way, excluding ground travel and fuel stop (East coast)
    - Cost ~$32,000 (charter $60,000-120,000)
Impact On Staff/Process

- Increased dry run fly outs (n=3)
  - Avg annual fly out dry run 2-3/yr
Post Transplant Treatment Issues

- Initially experienced delays in payor treatment approval for Genotype 2/3 pts due to previous paucity of literature regarding therapy post transplant
  - G1A/B approval 2-3 weeks
  - G2/3 approval on resubmission (up to 53 days)
Post Transplant Treatment Issues

• Since initiating this protocol, our institutional experience and increased availability of pangenotypic therapies has led to automatic approval in all cases
• Increased education of major payors along with decreased treatment costs has significantly improved access
  • Previous rx cost $60-80K
  • Recent contract negotiations $30-40K
What We’ve Learned So Far

- 4.1% of the donor population is HCV viremic*; in the climate of Region 5, HCV D+/R- donors are an acceptable resource
- The risk of the unknown “gaps” in transplanting these organs appears to be significantly outweighed by the benefit of increased access to “early” transplantation
- Aggressive staff education and thorough informed patient consent is critical
- Payor education and reduction in treatment cost, along with increased availability of pan-genotypic therapies, has significantly lowered previous perceived barriers to utilization of these organs

*These are awesome organs...They don’t belong in the bucket!

*Levitsky, J et al AJT 2017; 17: 2790-2802
Shout Out To My Peeps

Shiro Fujita MD, PhD
Ivan Zendejas, MD
Manuel Rodriguez, MD
Shout Out To My Peeps

Richard Gilroy, MD
Michael Charlton, MD
Buff Harmston, MD
Rob Jones, MD
EJ Frech, MD
Mark Boschert, MD
Lance Lindbergh, PharmD
Because At The End of the Day, This Is What It’s All About...