





The THINKER trial: Transplanting Hepatitis-C Infected Kidneys Into Hepatitis-C Negative Kidney Recipients

Vishnu Potluri, MD MPH
Renal Division
University of Pennsylvania






Disclosures

- I will be discussing off-label use of an FDA-approved drug (Grazoprevir/Elbasvir – Zepatier)
- This study is supported by an investigator-initiated grant from Merck.
- I will be discussing use of laboratory-derived test for testing of HCV genotype
- I am funded through the American Society of Nephrology, Ben Lipps Fellows Grant.






Increasing Wait-time to transplant



Deceased Donors by Age: Increasing number of younger donors

SRTR Annual Data Report: 2016

Opioid Epidemic: Unfortunate reason for increase in transplant volume


- Increase in number of organ donors who died from drug overdose
 - New England Organ Bank
 - 254% increase between 2012-16
 - Resulted in ~300 additional transplants
- 224 transplants from donors who were HCV +
 - 20 HCV + transplants in 2012; 80 in 2016!

Most HCV + kidneys get discarded

Disposition of Kidney Pairs	No. of Donors (%)	No. of Kidneys Discarded	Median Kidney Donor Profile Index (IQR)	Estimated Additional Graft-Years Obtainable by Transplanting Both Kidneys		
				1-Yr Survival	3-Yr Survival	5-Yr Survival
Both kidneys discarded	1718 (52.5)	3436	0.85 (0.67-0.96)	3000	7637	10,301
1 kidney transplanted, 1 discarded	708 (21.6)	708	0.71 (0.54-0.87)	636	1675	2,361
Both kidneys transplanted	847 (25.9)	0	0.60 (0.43-0.77)	—	—	—

Reese. NEJM. 2016



Kidney Donor Profile Index (KDPI): Measure of Organ Quality

- HCV positivity can have a significant impact on KDPI
- However, KDPI was published in 2009:
 - Used data from 1995-2005
- When compared to 2005:
 - Most donors with HCV now are younger

Rao. Transplantation. 2009

Exciting Era for Hepatitis C Treatment: Multiple New Medications in the last few years!

1990 1995 2000 2005 2010 2015 2020

What if the recipient is also hepatitis C positive?

- Already being practiced...
- Patients who are HCV + and on dialysis
 - Will have a shorter time to transplant if they choose kidneys that are HCV +

C-SURFER Trial: Elbasvir-Grazoprevir is effective in CKD 4/5 for Genotype 1a/b

Baseline viral load	50/50	100.0 (92.9-100.0)
≤800000 IU/mL	65/66	98.5 (91.8-100.0)
>800000 IU/mL		
Previous HCV treatment status		
Naïve	96/96	100.0 (96.2-100.0)
Experienced	19/20	95.0 (75.1-99.9)
Dialysis		
Yes	86/87	98.9 (93.8-100.0)
No	29/29	100.0 (88.1-100.0)
Diabetes		
Yes	40/41	97.6 (87.1-99.9)
No	75/75	100.0 (95.2-100.0)
Chronic kidney disease stage		
Stage 4	22/22	100.0 (84.6-100.0)
Stage 5	93/94	98.9 (94.2-100.0)

80 90 100 SVR12 (%[95% CI])

Roth. Lancet. 2015

THINKER Trial

- Funding: Merck
- 1st line therapy:
 - Elbasvir-Grazoprevir (Zepatier)
- Back-up treatment option if 1st line does not work
- 1 tablet, once a day for 3 months
- Wait an additional 3 months after therapy before deemed as cured

THINKER Trial: Inclusion Criteria

- On dialysis for ≤18 months
- Have ≤18 months of waiting time
- No available living kidney donor
- Only listed for a kidney transplant
- Blood group A, B, or O
- Aged 40-65 years of age
- PRA level ≤97%
- Able to travel to the University of Pennsylvania for routine post-transplant visits and study visits
- Not using illegal drugs
- Weigh at least 110 lbs



THINKER Trial: Exclusion Criteria

- Have liver disease
- Have serious heart problems
 - Because ineligible for liver transplant if this complication develops
- Have a specific type of kidney disease that is likely to come back after transplant (i.e., primary FSGS)
- Have HIV
- Are blood group AB
- Pregnant or nursing (lactating) women
- Unable to take tacrolimus after transplantation
- Waitlisted for more than just a kidney transplant

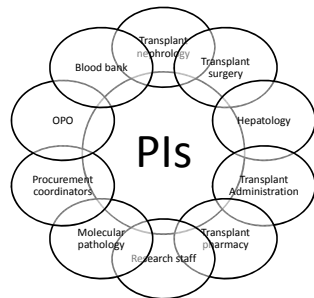


THINKER Trial: Why did we choose Genotype 1?

- It is the most common genotype
- Elbasvir-Grazoprevir works for genotype 1
- Patients can have delayed graft function and need dialysis post transplant
- Elbasvir-grazoprevir can be used in renal failure



Who are the stakeholders?



Slide courtesy of Dr. Reese



How do we consent patients?



- Educational sessions to provide more information
- Informal and patients have the opportunity to ask questions
- Discuss treatment options, cure rates, post-transplant logistics, unknowns
- Take consent with them home



Additional Protections

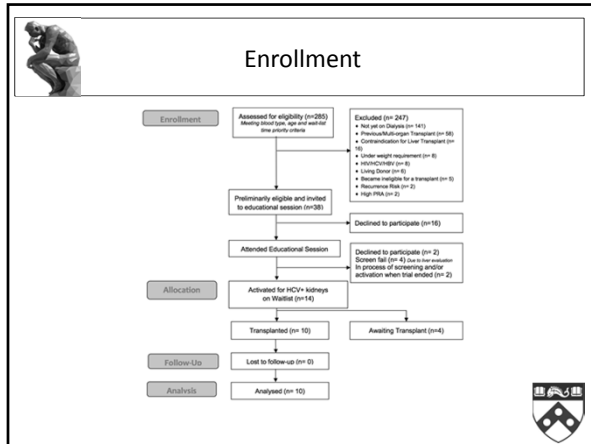
- We only use kidneys that are of good quality from donors with Hepatitis C
 - Younger
 - Few health problems
 - Genotype 1
- We start treatment for HCV immediately after confirming the presence of HCV RNA
 - Back up treatment
- Exclude patients with liver or cardiac disease
 - Evaluated by transplant hepatologist and undergo a fibroscan



Frequent Questions

- Will I get Hepatitis C?
- What is my risk of transmission of infection?
- What will happen if I don't get cured?
- What will happen to my regular wait-time on the transplant list?
- What is the risk for other viral infections?
- Will immunosuppression affect the treatment of hepatitis C?



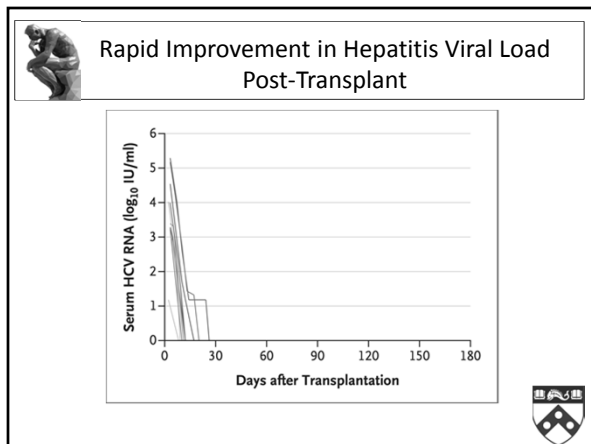
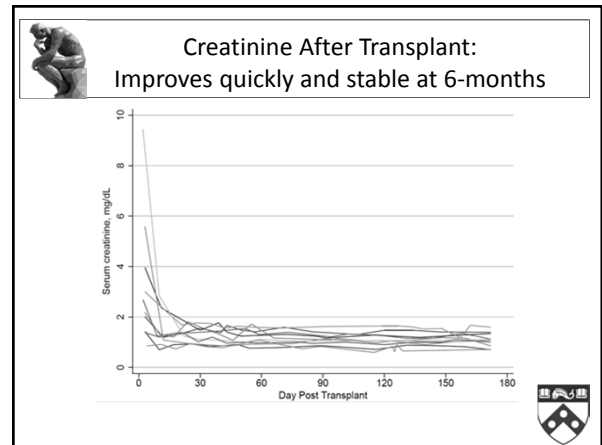


Recipient Characteristics

Age	Gender	Race	Etiology of ESRD	Liver stiffness, kPa†	Mode of dialysis	BMI	Waiting time at enrollment, days	Time from enrollment to transplant, days
65	Female	White	Interstitial nephritis	4.2	HD	29.2	169	11
50	Male	Black	Hypertension	5.6	HD	35.8	324	24
63	Female	White	Polycystic	7.1	HD	20.6	232	57
62	Female	White	Diabetes	6.1	HD	27.4	358	80
63	Male	Asian	IgA Nephropathy	5.1	PD	27.8	400	59
53	Male	White	Diabetes	5.6	HD	29.3	525	53
56	Male	White	IgA Nephropathy	4.9	HD	28.6	200	110
51	Female	White	Anatomical	4	HD	30.3	193	100
43	Male	Black	Secondary FSGS	6.1	HD	40.1	266	130
63	Female	White	Diabetes	6.7	PD	31.7	347	56

Donor Characteristics

Race	Gender	OPTN/UNOS region	Age	Cause of death	Mechanism of death	Terminal creatinine, mg/dL	DCDD	Cold ischemia time, hours:minutes	KDPI†
White	Male	10	46	Anoxia	Cardiovascular	0.5	No	22:30	48%
White	Female	3	28	Anoxia	Drug intoxication	0.5	No	20:30	32%
White	Male	2	31	Anoxia	Drug intoxication	1.4	No	13:14	46%
White	Female	2	45	CVA	Intra-cranial hemorrhage	1.0	No	10:45	73%
White	Male	10	46	Anoxia	Cardiovascular	0.5	No	16:31	48%
White	Female	3	28	Anoxia	Drug intoxication	0.5	No	27:45	32%
White	Male	2	29	Anoxia	Drug intoxication	0.79	No	9:01	35%
White	Male	2	30	Anoxia	Drug intoxication	1.4	Yes	16:26	58%
White	Male	2	25	Anoxia	Drug intoxication	1.24	No	13:20	23%
White	Male	2	32	Anoxia	Drug intoxication	0.6	Yes	13:01	37%



Adverse Events

SAE	Category	Start Date	Stop Date	Outcome	Severity/Grade	Related*	Expected	Action Taken
Intra-operative Bleeding (nasal; related to anesthesia trauma)	Procedural Complications	7/28/16	7/28/16	Resolved	3	Unrelated	No	None
Post-op re-intubation/failed extubation	Procedural Complications	7/24/16	7/24/16	Resolved	3	Unrelated	No	None
Post-op re-intubation/failed extubation	Procedural Complications	8/4/16	8/4/16	Resolved	3	Unrelated	No	None
Pneumonia	Respiratory, Thoracic	9/15/16	9/15/16	Resolved	3	Unrelated	No	None
Hyperkalemia	Metabolism and Nutritional Disorder	9/30/16	9/30/16	Resolved	2	Unrelated	No	None
Small bowel obstruction	Gastrointestinal disorder	12/2/16	12/3/16	Resolved	2	Unrelated	No	None
Renal Pelvic Mass & Native Nephrectomy	Renal Disorder	10/11/16	1/19/17	Resolved	2	Unrelated	No	None
Hyperparathyroidism; Parathyroidectomy	Metabolism and Nutritional Disorder	3/15/17	3/17/17	Resolved	3	Unrelated	No	None
Focal segmental glomerulosclerosis	Renal disorder	4/7/17		Ongoing	3	Possible	No	Angiotensin receptor blocker



THINKER: Where we are now

- Phase 1 = 10 transplants (published)
- Phase 2 = 10 transplants (completed)
- Phase 3 = 20 transplants (ongoing)



We are not alone! EXPANDER-1 Trial at Hopkins – Similar Results

HCV Donors	D1	D2	D3	D4	D5	D6	D7	D8
Age, years	21	26	38	30	42	35	30	23
Sex	Female	Female	Female	Male	Male	Male	Female	Male
Race	White	White	White	White	White	White	White	White
Body mass index	28	29	27	28	30	26	20	24
Cause of death	Trauma	Overdose	Trauma	Alcohol	Trauma	Overdose	Overdose	Overdose
Kidney donor profile index	45	43	60	47	42	41	50	34
HCV RNA (IU/mL)	467	104	<15*	46,733	62,409	4,645,289	2,090,042	1,760,000
HCV Genotype(s)	ND	ND	ND	1a/3a	1a	1a	3a	In process
HCV Recipients	R1	R2	R3	R4	R5	R6	R7	R8
Age, years	71	71	65	57	72	71	74	61
Race	White	White	White	White	White	Asian	White	Black
Sex	Male	Female	Male	Male	Male	Male	Female	Male
Blood type	O	O	AB	O	O	B	O	O
Kidney failure cause	Polycystic	Interstitial Nephritis	Lithium toxicity	Glomerulonephritis	NSAID toxicity	IgA Nephropathy	Polycystic	Diabetes

Results not yet published
Durand. ATC. 2017.



What does the future look like? At times like these I turn to great thinkers..



“Difficult to see.
Always in motion is the future..”
- Yoda

- Newer pan-genotypic medications are now being approved!
 - Might not have to restrict donors to Genotype 1
- We need to replicate results in larger cohorts
- Will price of HCV therapy change?
- How will transplant nephrologists react?
- Risk tolerance for small volume centers?



Next Steps

- Real World Feasibility
 - Will private insurance pay for these medications?
 - Changes in policy and organ allocation
- Expand eligible recipient pool
 - Restricted age to 40-65 years in THINKER
- Expand organ donor pool for HCV
 - Should we tolerate a higher creatinine at donation?



What does this mean for other organs? Heart??

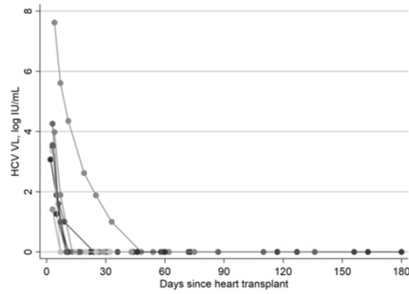
- USHER Trial at Penn
- Heart Transplant
- Results not yet published
 - (American Transplant Conference 2018)
- 9 transplants performed (Median wait-time 31 days)
- 2/9 cured (reached sustained viral response)
- 7/9 undetectable levels

Results Not Yet Published
McLean. ATC. 2018.





What does this mean for other organs? Heart??



Results Not Yet Published
McLean. ATC. 2018.



Acknowledgement

- Thank you ANNA!
- Pls: Peter Reese, MD & David Goldberg, MD
 - Peter Abt, MD; Emily Blumberg, MD
 - Roy Bloom, Deirdre Sawinski
 - Viviana Van Deerlin, MD, PhD and the molecular pathology lab
 - K. Rajender Reddy, MD
 - Susanna Nazarian, MD, PhD; Matthew Levine, MD, PhD; Paige Porrett, MD, PhD; Ali Naji, MD, PhD
 - Simin Goral, MD; Maryann Lim, MD; Melissa Bleicher, MD
 - Jennifer Trofe-Clark, PharmD
 - Rick Hasz, BS and Larry Suplee
 - Anna Sicilia, BS; Maureen McCauley, BS; Adam Mussell, MS
- My Wife for tolerating me!



QUESTIONS?

