Hepatitis C Virus In Patients with Renal Insufficiency

David L. Thomas, MD, MPH
Professor of Medicine
Director, Division of Infectious Diseases
The Johns Hopkins University School of Medicine
Baltimore, Maryland

IAS–USA

Learning Objectives

After attending this presentation, participants will be able to:

- **Compare the doses of medication in patients with renal failure to those without**
- **Identify which patients with renal failure might benefit from treatment**

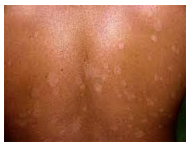
HCV with renal failure

- A 43-year-old African American man with genotype 1A chronic HCV presented to the clinic. He had HTN and HCV. Prior IDU and ETOH. Married. Just had fistula placed for dialysis that started 6 months ago. HIV negative. Exam: 156/92; RRR 2/6 SEM; hyperpigmented annular patches on extremities and trunk; fistula with thrill.
- 1a; HCV 6.2 log IU/ml; HIV neg; creat 9; PLT 133K; AST 67 IU/ml; ALT 50 IU/ml; TB 0.5; Alb 4.1. INR 1. HBsAg neg.

Slide 4 of 23

HCV with renal failure

- Each time you try to describe the data on HCV treatment in renal failure he interrupts you to ask about his rash. It looks like this:



Slide 5 of 23

What is the next step?

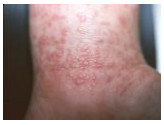
2% 1. Urine porphyrins
21% 2. Serum cryoglobulin titer
29% 3. RPR
19% 4. Bx for lichen planus
25% 5. KOH
5% 6. Tell him to stop interrupting

Slide 6 of 23

Compare

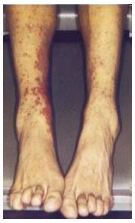
Porphyria cutanea tarda

Lichen planus



blogspot.com,

Cryoglobulin vasculitis



O'Connor Mayo Clin Proc 1998

Slide 7 of 23

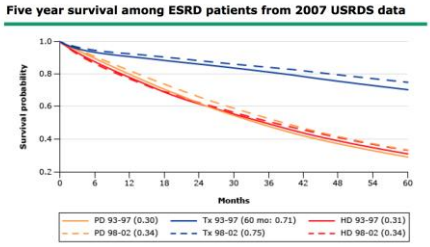
1a chronic hep C with renal failure

- KOH was pos; RPR neg. Responded to terbinafine.
- What would you do next?

1. Sof/LDV x 12 weeks
2. PrOD x 12 weeks
3. PrOD and GFR adjusted RBV x 12 weeks
4. Peg RBV x 48 weeks
5. Transplant

Slide 8 of 23

Transplant improves survival



From Up To Date 2015; U.S. Renal Data System, USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2009.

Slide 9 of 23

1a chronic hep C with renal failure

- You were so busy treating his tinea you forgot to finish your history. Transplant surgeon calls and tells you he is a Jehovah's Witness, and "he won't touch him" unless he can transfuse him. Meanwhile his transient elastography comes back 14.5 kPa. Now what?

1. Sof/LDV x 12 weeks
2. PrOD x 12 weeks
3. PrOD and GFR-adjusted RBV x 12 weeks
4. Peg RBV/week x 48 weeks
5. Terbinafine and ribavirin x 12 weeks

Slide 10 of 23

1a chronic hep C with renal failure

- You were so busy treating his tinea you forgot to finish your history. Transplant surgeon calls and tells you he is a Jehovah's Witness, and "he won't touch him" unless he can transfuse him. Meanwhile his transient elastography comes back 14.5 kPa. Now what?

19% 1. Sof/LDV x 12 weeks
5% 2. PrOD x 12 weeks
73% 3. PrOD and GFR-adjusted RBV x 12 weeks
0% 4. Peg RBV/week x 48 weeks
3% 5. Terbinafine and ribavirin x 12 weeks

Slide 11 of 23

SOF/LDV metabolism and the kidney

Sofosbuvir: 80% of dose excreted in urine (most as 007)
- 007 $t_{1/2}$ is 27 hrs

	AUC (% increase) compared to GFR >80		
	Mild	Moderate	Severe
SOF	61%	107%	171%
331007	55%	85%	451%

- HD: 12-20 fold increase in 007 AUC

Ledipasvir: Primarily eliminated in feces (>70%)
- Limited (<2.0%) urinary excretion
- No changes in exposure with GFR <30

Slide courtesy D Wyles. Cornpropst M. #1101 EASL 2012. Kirby B. #O_22 HCV Clin Pharm Workshop 2013. Ledipasvir/sofosbuvir package insert. Sofosbuvir package insert.

Slide 12 of 23

3D (PrOD) regimen in ESRD

- All components: hepatic metabolism
  - <2% excreted in urine

Table 4. Effect of Severe Renal Impairment on Pharmacokinetic Parameters of DAAs and Ritonavir

	Parameter	ABT-450	Ritonavir	ABT-267	ABT-333
Severe Impairment (CLcr: 15 – 29 mL/min)	C_{max}	↔	↑ 66%	↔	↔
	AUC	↑ 45%	↑ 114%	↔	↑ 50%

↑ = increase; ↔ = less than 20% change

Slide courtesy D Wyles; PrOD package insert.

Slide 13 of 23

HCV treatment in renal insufficiency
AASLD/IDSA/IAS–USA HCV Guidance

Renal Impairment	eGFR / CrCl level (mL/min)	PEG-IFN	RBV	Sofosbuvir	Ledipasvir	Daclatasvir	Ombitasvir	Dasabuvir	Paritaprevir	Simeprevir
Mild	50-80	PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1.5 µg/kg	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard

Slide 14 of 23

HCV treatment in renal insufficiency
AASLD/IDSA/IAS–USA HCV Guidance

Renal Impairment	eGFR / CrCl level (mL/min)	PEG-IFN	RBV	Sofosbuvir	Ledipasvir	Daclatasvir	Ombitasvir	Dasabuvir	Paritaprevir	Simeprevir
Moderate	30-50	PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1 µg/kg (25% reduction)	Alternating doses 200 mg and 400 mg every other day	Standard	Standard	Standard	Standard	Standard	Standard	Standard

Slide 15 of 23

HCV treatment in renal insufficiency
AASLD/IDSA/IAS–USA HCV Guidance

Renal Impairment	eGFR / CrCl level (mL/min)	PEG-IFN	RBV	Sofosbuvir	Ledipasvir	Daclatasvir	Ombitasvir	Dasabuvir	Paritaprevir	Simeprevir
Severe	<30	PEG-IFN (2a) 135 µg; PEG-IFN (2b) 1 µg/kg (50% reduction)	200 mg/d	Limited data available	Data not available	Limited data available	Limited data available	Limited data available	Limited data available	Standard

Slide 16 of 23

HCV treatment in renal insufficiency
AASLD/IDSA/IAS–USA HCV Guidance

Renal Impairment	eGFR / CrCl level (mL/min)	PEG-IFN	RBV	Sofosbuvir	Ledipasvir	Daclatasvir	Ombitasvir	Dasabuvir	Paritaprevir	Simeprevir
ESRD with HD		PEG-IFN (2a) 135 µg/wk or PEG-IFN (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk	200 mg/d	Limited data available	Data not available	Limited data available	Limited data available	Limited data available	Limited data available	Limited data available

Slide 17 of 23

HCV treatment in renal insufficiency
AASLD/IDSA/IAS–USA HCV Guidance

For patients with CrCl below 30 mL/min who do not have cirrhosis but for whom the urgency to treat (or retreat) is high and renal transplant is not an immediate option, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with twice-daily dosed dasabuvir (250 mg) (for HCV genotype 1b infection) or without dasabuvir (for HCV genotype 4 infection) is recommended. However, this recommendation is based on limited data on safety and efficacy.

Rating: Class IIb, Level B

For HCV genotype 1a infection, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with RBV at reduced doses (200 mg thrice weekly to daily*) is recommended. However, caution is recommended in this group, owing to the potential for hemolysis in this population, and RBV should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

Rating: Class IIb, Level B

Slide 18 of 23

Limited use of SOF in renal disease

Pilot study of 200 mg SOF and 200 mg RBV in those with severe renal impairment (eGFR<30) or on HD

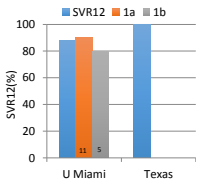
- 10 non-cirrhotic GT1 or 3 subjects
  - 4 (40%) SVR 12
  - 5 changed RBV dose

Gane EJ. #966 AASLD 2014.

Slide 19 of 23

Limited use of SOF in renal disease

- Miami: 16 pts- GFR <15 or HD
  - 42% naïve, 58% cirrhotic
  - SOF 200mg QD + SMV 150mg QD; no RBV
    - 3 pts: SOF 400mg QOD with SMV
- Texas: 11pts- GFR<30 or HD
  - 82% naïve, 47% cirrhosis
  - SOF 400mg QD + SMV 150mg QD; no RBV
  - 88% on HD

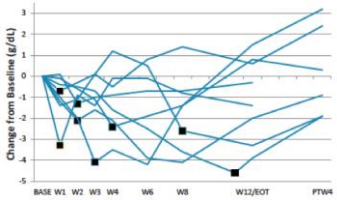


Czul F. #92 EASL 2015. Nazzario HE. #614 EASL 2015.

Slide 20 of 23

PrOD and RBV in ESRD

- 20 pts naïve
  - 100% SVR4 in 10
    - with RBV dose interruption

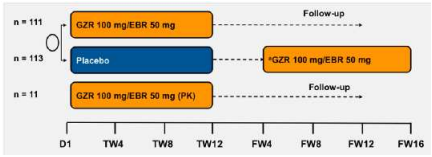


RUBY-I **Pockros P. EASL 2015.**

Slide 21 of 23

Grazoprevir/Elbasvir in ESRD*

- GZR/EBR: both <1% renal elimination
  - No dose adjustment needed



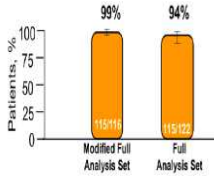
- 73% male, 46% AA, 80% naïve, 52% 1a, 6% cirrhosis
- 81% CKD stage 5 (GFR <15 or HD)

* Investigational drugs

C-SURFER **Roth D. # EASL 2015.**

Slide 22 of 23

Grazoprevir/Elbasvir in ESRD

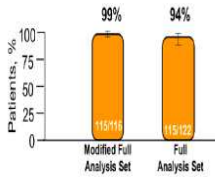


1 viral relapse
6 discontinuations

C-SURFER Roth D. # EASL 2015.

Slide 23 of 23

Grazoprevir/Elbasvir in ESRD



1 viral relapse
6 discontinuations

C-SURFER Roth D. # EASL 2015.

	GZR/EBR (ITG) (n = 111)	Placebo (DTG) (n = 113)	Difference in % Estimate (95% CI)
AEs,* n (%)	84 (75.7)	95 (84.1)	−8.3 (−18.9, 2.2)
Headache	19 (17.1)	19 (16.8)	0.3 (−9.6, 10.4)
Nausea	17 (15.3)	18 (15.9)	−0.6 (−10.3, 9.1)
Fatigue	11 (9.9)	17 (15.0)	−5.1 (−14.1, 3.7)
Insomnia	7 (6.3)	12 (10.6)	−4.3 (−12.2, 3.2)
Dizziness	6 (5.4)	18 (15.9)	−10.5 (−19.1, −2.6)
Diarrhea	6 (5.4)	15 (13.3)	−7.8 (−16.1, −0.2)
Serious AEs, n (%)	16* (14.4)	19 (16.8)	−1.5 (11.2, 8.1)
Discon due to an AE, n (%)	0 (0)	5 (4.4)	−4.4 (10.0, −1.0)
Deaths,* n (%)	1 (0.9)	3 (2.7)	−1.8 (−6.7, 2.5)

	GZR/EBR (ITG) 12 weeks (n = 111)	Placebo (DTG) 12 weeks (n = 113)	Difference in % Estimate (95% CI)
ALT, n (%)			
1.1-2.5 × baseline	2 (1.8)	36 (31.9)	−30.1 (−39.4, −21.5)
>2.5-5 × baseline	1 (0.9)	6 (5.3)	−4.4 (−10.3, 0.2)
>5× baseline	0 (0)	1 (0.9)	−1.1 (−6.3, 3.2)
AST, n (%)			
1.1-2.5 × baseline	4 (3.6)	38 (33.6)	−30.0 (−39.6, −21.0)
>2.5 × baseline	0 (0)	4 (3.5)	−4.6 (−11.3, −0.2)
Total bilirubin,† n (%)			
>2.5-5.0 × baseline	1 (0.9)	3 (2.7)	−1.8 (−6.7, 2.5)
>5.0 × baseline	0 (0)	0 (0)	0.0 (−3.3, 3.4)
Alkaline phosphatase, n (%)			
1.1-2.5 × baseline	42 (37.8)	36 (31.9)	6.0 (−6.8, 18.3)
>2.5 × baseline	0 (0)	0 (0)	0.0 (−3.3, 3.4)

Slide 24 of 23

HCV in renal insufficiency

- No issues with GFR above 50
- Lower than 30-50, dose adjust RBV with more renal insufficiency and watch for anemia with coronary disease
- Avoid SOF with GFR < 30 (for now)
- Transplant when you can
- 1b PrOD; 2016, consider grazoprevir/elbasvir for 1a