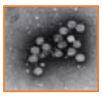

Novel Therapies in the Management of Hepatitis C Virus Infection

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Disclosures

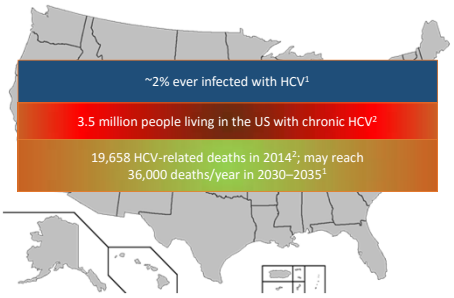
- Scientific Advisory Board: Merck and Co.; Abbvie; Bristol-Myers Squibb.
- Consultant: Merck and Co.

Objectives

- Brief overview of HCV infection
- Review the results of recent DAA trials conducted in the CKD/ESRD patient population.
- Provide a platform for a discussion on the best timing for treatment of HCV-infected CKD/ESRD patients.

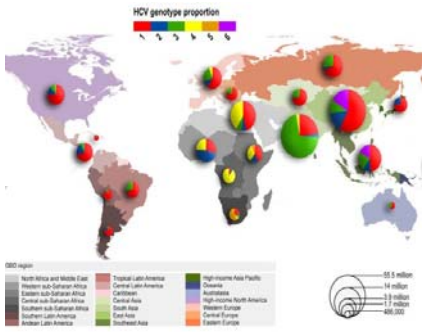
The "Lingo"

- SVR_{12}- sustained viral response at 12 weeks after completing antiviral medication. Patients that test negative for virus at week 12 post therapy are considered cured of HCV. Patients with detectable virus after a SVR_{12} have been re-infected.
- DAA- direct acting antivirals. These are the new generation of HCV meds that followed the interferon era and target specific sites on the HCV genome.
- Genotype- there are at least 6 different genotypes of the virus with varying penetration globally.
- Liver injury- Stage 4 liver disease represents cirrhosis. Patients can have stage 0-4. Non-invasive tests are available that can obviate the need for a biopsy in many cases.



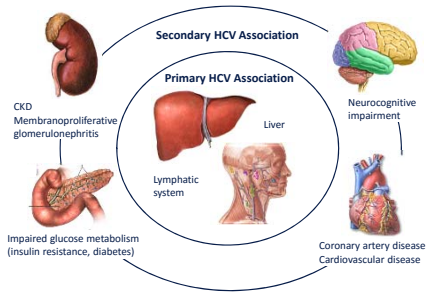
1. www.hepatitisc.uw.edu/pdf/screening-diagnosis/epidemiology-us/core-concept/all 2. www.cdc.gov/hepatitis/HCV/HCVfaq.htm

Global Variance in HCV Genotypes



Groeger J, Flaxman AD, Wiersma ST. Hepatology. 2013;57(4):1333-42.

HCV as a Systemic Infection Affecting Multiple Organ Systems



Gill K, et al. *Hepatol Int*. 2016;10(3):415-423.

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DOPPS Analysis of Hepatitis C Infection in Patients on Hemodialysis

- International, prospective cohort study of HD patients.
- n=76,689 adults enrolled between 1996-2015 in 21 countries.
- Compared anti-HCV antibody positive with negative patients. No NAT data or liver histology available.
- Evaluated mortality, hospitalization, and health-related quality-of-life scores.

Goodkin, et al. CJASN 2016 doi: 10.2215/CJN.07940716

DOPPS Hospitalizations and Mortality Data

Table 3. Hospitalization events for HCV+ versus HCV− patients (DOPPS phases 1–5, 1996–2015)

Hospitalization Type	No. of Events	Crude Rate[a]	Unadjusted HR[b] (95% CI)	Adjusted HR[c] (95% CI)
All-cause hospitalization	38,895	626.7	1.06 (1.02 to 1.11)[d]	1.09 (1.04 to 1.13)[d]
Cardiovascular[e]	14,525	187.2	1.04 (0.98 to 1.11)	1.10 (1.03 to 1.17)[d]
Stroke	2074	23.3	0.97 (0.83 to 1.13)	1.08 (0.92 to 1.27)
Myocardial infarction	2208	24.8	0.97 (0.82 to 1.15)	1.05 (0.88 to 1.25)
Infection[f]	9597	116.4	1.07 (0.99 to 1.16)	1.08 (1.00 to 1.18)
Sepsis	2592	29.3	1.05 (0.89 to 1.23)	1.06 (0.90 to 1.25)
Pneumonia	2209	24.9	1.14 (0.97 to 1.33)	1.15 (0.98 to 1.35)
Hepatic-related[g]	231	2.6	5.51 (4.09 to 7.44)[d]	4.40 (3.14 to 6.15)[d]

Table 2. Mortality for HCV+ versus HCV− patients (DOPPS phases 1–5, 1996–2015)

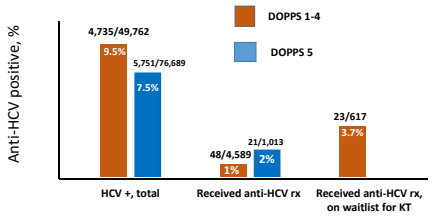
Event	No. of Events	Crude Rate[a]	Unadjusted HR[b] (95% CI)	Adjusted HR[c] (95% CI)
All-cause mortality	15,807	139.5	1.02 (0.95 to 1.09)	1.12 (1.05 to 1.20)[d]
Cardiovascular	6790	65.8	0.97 (0.87 to 1.07)	1.10 (0.98 to 1.22)
Infection	2187	21.2	1.05 (0.88 to 1.27)	1.11 (0.91 to 1.34)
Hepatic-related[g]	113	1.1	5.88 (3.84 to 8.99)[d]	5.90 (3.67 to 9.50)[d]

n= 73,577 patients included in the all-cause models. d; p<0.05

Goodkin, et al. CJASN 2016 doi: 10.2215/CJN.07940716

DOPPS: HCV Treatment in Dialysis Patients

- DOPPS 1-4: 1996–2011; DOPPS 5: 2012-2015
- IFN and ribavirin in DOPPS 1-4; DAAs used in some of the DOPPS 5 patients



Goodkin DA et al. *Am J Nephrol*. 2013;38:405-412; Goodkin CJASN 2016, doi: 10.2215/CJN.07940716

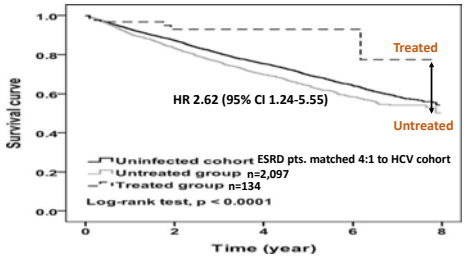
DOPPS Conclusions

"In summary, it appears erroneous to assume that HCV infection among patients on HD can be ignored because these patients will not live long enough to develop undesirable consequences.

HCV infection essentially goes untreated among patients on HD in 21 countries, yet it is associated with higher risks of mortality, hospitalization, liver complications, gastrointestinal bleeding, and anemia related sequelae, as well as a variety of undesirable quality of life scores, including greater pain and worse vitality, depression, anorexia, and pruritis."

Goodkin, et al. CJASN 2016 doi: 10.2215/CJN.07940716

Impact of Treatment on Mortality in HCV-Infected ESRD Patients



Hsu, Yueh-Han; et al. Medicine. 2015;94(47):e2113

Does the level of kidney function affect treatment choices in HCV-infected CKD patients?

Direct-Acting Antiviral Drug Choices in Patients With Kidney Disease

Drug	Primary Metabolic Pathway	Recommendations from Package Insert and AASLD Guidelines
Sofosbuvir	Renal	Insufficient data for CrCl < 30 ml/min
Ledipasvir	Hepatic	Data not available for CrCl < 30 ml/min
Velpatasvir	Hepatic	Data not available for CrCl < 30 ml/min
Grazoprevir	Hepatic	No restrictions in CKD or ESRD
Elbasvir	Hepatic	No restrictions in CKD or ESRD
Daclatasvir	Hepatic	No restrictions
Simeprevir	Hepatic	Limited data for ESRD/HD
Paritaprevir/r	Hepatic	No dose adjustments necessary for CKD or ESRD/HD. Use Ribavirin with caution
Ombitasvir	Hepatic	
Dasabuvir	Hepatic	

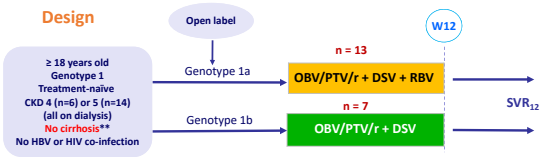
Sofosbuvir (Sovaldi®) prescribing information (PI); ledipasvir/sofosbuvir (Harvoni®) PI; elbasvir/grazoprevir (Zepatier™) PI; daclatasvir (Daklinza™) PI; simeprevir (Olysio®) PI; paritaprevir/ritonavir/ombitasvir, dasabuvir (Viekira Pak) PI.

Studies Providing Data on DAAs in HCV-Infected ESRD Patients

- RUBY-1(Cohort 1 and 2)
- RUBY-2
- C-SURFER
- EXPEDITION- IV

RUBY-I Study: Ombitasvir/Paritaprevir/ritonavir + Dasabuvir ± RBV for HCV Genotype 1 Patients with CKD

Design

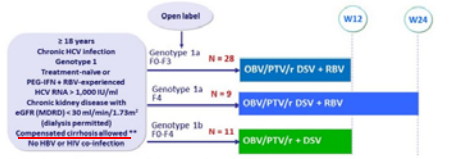


Results

- SVR_{12}: 18/20 patients (90%)
- SVR_{12} in 11/13 (85%) genotype 1a patients
- 9/13 genotype 1a patients had to interrupt ribavirin treatment due to anemia- 4 required EPO.

Pockros PJ. Gastroenterology 2016;150:1590-8

RUBY-I Study, Cohort 2: Ombitasvir/paritaprevir/ritonavir + Dasabuvir ± RBV for HCV Genotype 1 with Renal Impairment



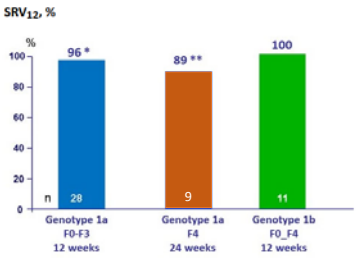
** Liver biopsy (Metavir = F3, Ishak score = 4) or F ibroscan < 12.5 kPa or FibroTest = 0.72 + APRI = 2

Treatment regimens

- Co-formulated ombitasvir (OBV)/ paritaprevir (PTV)/ rironavir (r): 25/150/100 mg qd = 2 tablets
- Dasabuvir (DSV): 250 mg bid ; RBV 200 mg qd (genotype 1a)

Vierling JM. AASLD 2016, Abs. 886

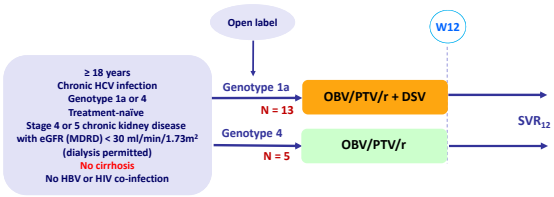
RUBY-I Study, Cohort 2: Ombitasvir/paritaprevir/ritonavir + Dasabuvir ± RBV for HCV Genotype 1 with Renal Impairment



* on - treatment breakthrough (non compliance , stopped taking all study drugs on D73 of treatment)
** discontinuation of study drug at D6 due to an adverse event (volvulus) not related to study drug

Vierling JM. AASLD 2016, Abs. 886

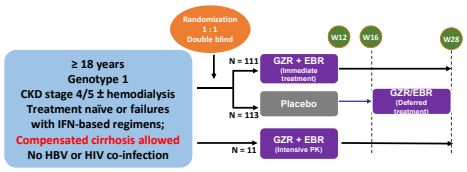
RUBY-II Study: Ombitasvir/paritaprevir/ritonavir + Dasabuvir for HCV Genotype 1a or 4 with Stage 4/5/5D CKD



	Genotype 1a (N = 13) OBV/PTV/r + DSV	Genotype 4 (N = 5) OBV/PTV/r
SVR_{12}, %		
ITT	100	80 *
mITT	100	100

Gane E. AASLD 2016, Abs. 935

C-SURFER: Grazoprevir + Elbasvir in HCV Genotype 1 Patients with CKD 4/5/5D



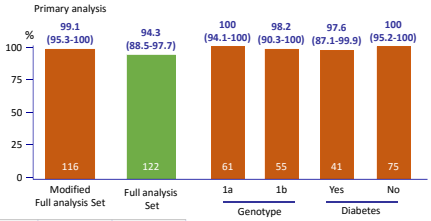
Objective

SVR_{12} (HCV RNA < 15 IU/ml) in immediate + PK groups:
45% historical response rate to IFN-based regimens used

Roth D et al. *Lancet.* 2015;386:1537-1545.

C-SURFER: SVR_{12} Rates

SVR_{12} (HCV RNA < 15 IU/ml), % (95% CI), mITT



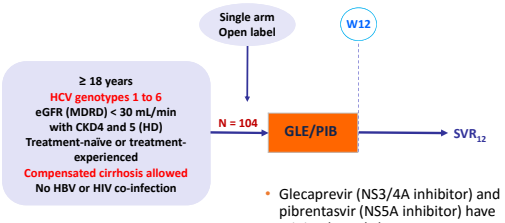
Relapse	1*	1
Discontinuation unrelated to treatment	0	6

Modified full analysis set excluded patients who died or discontinued for reasons unrelated to treatment

* Genotype 1b, non cirrhotic, CKD stage 5, NS5A RAV at baseline : L31M, at failure : L31M + Y93H

Roth D. Lancet 2015; Oct 6; 386:1537-45

Expedition-IV: Treatment of HCV-Infected CKD Patients with Glecaprevir and Pibrentasvir



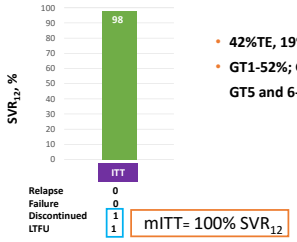
- Glecaprevir (NS3/4A inhibitor) and pibrentasvir (NS5A inhibitor) have minimal renal clearance.
- CKD 4: 13%; CKD 5: 87%; 82% HD

– GLE/PIB : 100/40 mg 3 tablets QD

- **Objective**
  - SVR_{12} (HCV RNA < 15 IU/mL)

Gane E. AASLD 2016, Abs. LB-11

Expedition-IV: Treatment of HCV-Infected CKD Patients with Pangenotypic Agents



- **42%TE, 19% comp cirrhosis**
- **GT1-52%; GT2-16%; GT3-11%; GT4-19%; GT5 and 6-1%**

mITT= 100% SVR_{12}

Gane, et al. AASLD, 2016

CDC Alert on HCV and Dialysis

- Between 2014 and 2015, the CDC has been contacted about 36 cases of acute HCV infection in 19 different dialysis clinics.
- HCV transmission between patients has been demonstrated at nine of those clinics so far, based on epidemiologic and viral-sequencing evidence.
- Lapses in infection control (eg, injection safety, environmental disinfection, and hand hygiene) were commonly identified at these facilities.

Questions to Consider at this Point

- In the context of the CDC Health Advisory alert from 2016 concerning cases of acute HCV, do we need to revisit this issue and:
  - Treat to **eradicate** the virus from the dialysis population AND/OR
  - **Continue with** "improved infection control practices to stop HCV transmission" as suggested by the CDC OR
  - **Consider isolation** of HCV patients (not recommended).
- If HCV-infected ESRD patients have improved survival with treatment, should all infected ESRD patients be considered for DAA treatment?

Example From a Large Dialysis Provider: Recommendations for Hepatitis C Evaluation and Treatment Algorithm

1) Is the patient a kidney transplant candidate?- if yes then contact the transplant center and document their recommendation for timing of treatment. Discuss with nephrologist and obtain final decision.
2) If NAT (+) and GT 1a, 1b or 4 and treatment naïve: move forward with the algorithm for treatment (no specialist).
3) If NAT (+) and GT 2, 3, 5, 6, mixed GT or treatment experienced (with DAA): consider specialist referral.
4) If HIV and HBsAg are both neg with normal plts and INR and APRI <0.4: begin treatment with Zepatier.
5) Follow labs monthly and then until SVR_{12} obtained. Refer to specialist for viral relapse.

The Case for Pre vs. Post Kidney Transplant HCV Therapy

In Favor of Pre

- Cure is probable and durable
- Likely to reduce the risk of:
  - progressive liver injury
  - post-transplant GN
  - new onset diabetes
- Avoid drug-drug interactions with IS post transplant

Favoring Post

- Can use HCV+ donor kidney
- Shorter wait time
- Less dialysis vintage
- Improved eGFR of the KTR allows for greater therapeutic options.

Summary

- Although the prevalence of HCV in HD patients is decreasing, it is still far greater than the general population and acute HCV infection due to patient-to-patient dialysis clinic transmission continues to occur.
- Treatment rates of HCV-infected dialysis patients lags far behind that of the general population.
- Nephrologists need to be drawn into this discussion and decision tree.
- Novel agents will soon be coming to the market that are pan-genotypic and safe for patients with kidney disease.
- HCV can be eliminated from the kidney disease population if we choose to do so.

Thank you!