A New Clinical Paradigm for Hepatitis C End-Stage Renal Disease Patients: Balancing Viral Eradication and Early Kidney Transplantation

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Abstract

The development of safe and effective direct-acting antiviral therapies for chronic hepatitis C infection has changed the clinical paradigm for the management of waitlisted kidney transplant patients. This is particularly striking when balancing early kidney transplantation with a hepatitis C positive kidney transplant versus viral eradication with direct-acting antiviral therapies. Moreover, the management of potential kidney transplant alone candidates has changed guidelines for transplanting hepatitis C patients in various stages of liver disease, since their liver health may now be improved with medical intervention. A variety of factors need to be considered in the care of these patients including: accurate liver staging, medication choice, timing of therapy in relation to kidney transplant, and potential medication interactions with immunosuppressive treatments. This clinical review provides an algorithm for the evaluation, triage, and treatment options for this unique cohort and provides guidelines for transplant professionals to effectively determine the optimal treatment plan of hepatitis C patients with chronic kidney failure.

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Introduction

We have witnessed dramatic advances in the therapy for chronic viral hepatitis C (HCV) since the approval of the first direct-acting anti-viral agent (DAA) in April of 2011 (1). There are now twelve FDA approved DAA agents combined in eight unique all oral regimens available on market (2).Treatment selection is dependent on the genotype of the virus, stage of liver disease, prior treatment history, potentially the presence of resistance-associated substitutions (RAS) and co-morbidities (3, 4). While early in the evolution of antiviral therapy, there were numerous "difficult to treat populations"; at present, most patients can anticipate a greater than ninety-percent likelihood of a sustained virologic response (SVR). "Special patient populations" has become a more appropriate term to describe subpopulations of patients for which additional consideration must be given to regimen selection and timing of therapy (5). Patients with end stage renal disease (ESRD) are such a special patient population. Treatment decisions for patients with co-morbid HCV and ESRD requires accurate staging of both liver and kidney disease, knowledge of FDA labeling for DAA regimens with reductions in creatinine clearance (CrCl), consideration of the patients' candidacy for kidney transplant, as well as, attention to patient education and shared decision-making.

The HCV positive ESRD population may have shorter waiting times as they are able to receive a kidney from a Hepatitis C viremic donor. This is one area in kidney transplantation where the supply of organs is sufficient to meet demand. The key is to better understand when an HCV viremic ESRD patient should receive treatment proximate to their kidney transplant and if deferring treatment in certain groups will improve their overall health by earlier kidney transplant, followed by HCV eradication. Forthcoming, we provide a clinical pathway that describes the current understanding of solitary kidney transplant in the HCV ESRD patient and also provides guidelines that attempt to balance the advantages of early kidney transplant with that of HCV treatment deferral.

Patient evaluation

The prevalence of HCV is higher amongst patients with chronic kidney disease (CKD) and those on renal replacement therapy (RRT) than the broader population (6). HCV is a known risk factor for the development of ESRD, a finding that was recently validated by review of REVEAL data which showed hazard ratio (HR) of 2.33 (95% confidence interval [CI], 1.40 to 3.89) for developing ESRD in individuals with HCV compared to non-HCV ESRD groups. Those with a high viral load (VL) >175,000IU/mL and genotype 1 disease are at even higher risk (7). There is a higher rate of false negative serologic testing in patients with ESRD and therefore, nucleic acid testing (NAT) testing should be considered even in the setting of negative serology (6) At this time, would like to notate that it is the Kidney Disease Improving Global Outcomes (KDIGO) guidelines are being updated including potential changes to

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NAT testing recommendations. It is possible for individuals with ESRD to have reduced or normal transaminases despite chronic infection, and has been proposed to be due to a variety of factors including hemodilution, viral filtration, or reduced pyridoxine levels. As summarized in Table 1, an appropriate patient evaluation must include a comprehensive assessment of clinical data related to viral factors, stage of the liver disease and kidney disease, review of extra-hepatic manifestations of HCV, kidney transplant candidacy and factors affecting organ access for transplant.

Table 1: Evaluation of the HCV positive ESRD Patient

Viral	Hepatic	Renal	Extra-hepatic	Organ access
RNA/Genotype	Grade of inflammation	Etiology	MPGN	ABO
RAS	Fibrosis stage	CKD stage	Vasculitis	PRA
Co-Infection HIV	Hepatic function	RRT	Lymphoma	Accrued time
Co-Infection HBV	Portal hypertension			Living donor
Treatment history	Co-morbid liver disease			
RAS= resistance associated substitution, CKD= chronic kidney disease, RRT = renal				
replacement therapy, ABO = blood type system, PRA= panel reactive antibody				

Critical to understanding whether a patient may be accepted as a kidney transplant candidate is an accurate assessment of the stage of hepatic fibrosis with the discriminating factor being the presence of cirrhosis and portal hypertension. Physical examination assessing for stigmata of advanced liver disease and basic laboratory data (platelet count, albumin, INR, bilirubin) may provide the clinician with an initial impression regarding the likelihood of cirrhosis and portal hypertension. Ultrasound imaging should be obtained to assess for a grossly nodular liver morphology, splenomegaly, and doppler flow in the portal vessels. However, our clinical experience is that reports are often ambiguous and confusing in the setting of peritoneal dialysis where dialysate may be erroneously labeled as “ascites” and with hepatic congestion from volume overload in ESRD, particularly in patients who are not yet on dialysis. The gold standard tool for this assessment remains transjugular liver biopsy (TJLbx) with portal pressure measurements to calculate the hepatic venous pressure gradient (HVPG) and histologic review. However, biopsy is invasive with associated risk (2-3% risk of hospitalization and 0.01% mortality) and subject to sampling error (8, 9). Alternative non-invasive methods of fibrosis assessment include clinical scores such as FIB-4 [age (years) x AST (U/L)/ platelet (10^9/L) x ALT (U/L)], biomarkers not yet commercially available, and radiologic modalities such as transient elastography, acoustic radiation force impulse imaging (ARFI), and magnetic resonance elastography (MRE), though they have not been specifically validated in this clinical setting of patients with (ESRD). Table 2 provides performance characteristics of such non-invasive modalities.

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Table 2. Reported Performance Characteristics for Liver Biopsy and Non-Invasive Tests for Liver Fibrosis in Chronic HCV Infection (10-18)

Test	Performance characteristics	References
Liver biopsy	Considered gold standard test Cirrhosis missed in 10 to 30% of cases with single bland biopsy	Manning & Afdhal, Gastroenterology 2008
Transient elastography	For ≥ F2 fibrosis, Se 70 Sp 84 For F4 fibrosis, Se 87 Sp 91	Talwalkar, et al, clin gastro hepatol, 2007 (also Castera, L., Gastroenterology, 2012 [table 4])
Fibrospect II	For ≥ F2 fibrosis, Score >0.36 Se 77 Sp73	Patel et al., J Heparol, 2004 (also table 3 Castera)
Fibrotest	For ≥ F2 fibrosis, Score >0.48 Se 75 Sp 85	Imbert-Bismut et al., Lancet 2001 (also table 3 Castera)

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Test	Performance characteristics	References
APRI score	For F3-4 fibrosis, score >0.7 Se 77 Sp 72 score >1.0 Se 76 Sp 72 score >2.0 Se 46 Sp 91	Chou et al., Annals IM, 2013 Castera, L., Gastroenterology, 2012 (table 3)
FIB-4 score	For F4 fibrosis, score <1.45 NPV 90% score >3.25 Sp 97 PPV 65	Sterling et al., Hepatology, 2006
ARFI	For ≥ F2 fibrosis, cutoff 1.44 m/s Se 85 Sp 76 For F4 fibrosis, cutoff 1.90 m/s Se 92 Sp 87	Crespo et al, J Hepatol, 2012

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Test	Performance characteristics	References
Magnetic resonance elastography (MRE)	For ≥ F2 fibrosis, cutoff 3.66 kPa Se 79 Sp 81 For F4 fibrosis, cutoff 4.71 kPa Se 91 Sp 81	Singh et al., Clin Gastroenterol Hepato, 2015

We propose an initial non-invasive assessment. If data is concordant and does not suggest advanced fibrosis, then further testing is not needed for staging. If the data is concordant and clear that there is portal hypertension further testing is not needed for staging. However, standard cirrhotic health maintenance guidelines should be followed in regards to screening for hepatocellular carcinoma (HCC) and for esophageal varices. If the data is concordant and suggestive of advanced fibrosis, or if the data is discordant, then further evaluation inclusive of invasive testing should be pursued to more precisely clarify the stage of disease. This should include TJLbx, endoscopic assessment for gastroesophageal varices, and dynamic imaging assessment for intraabdominal collaterals. Please add sentence: Note, that the risk of dynamic i.e. contrast imaging in patients who still make a significant amount of urine should be considered as contrast induced nephropathy may lead then to worsening of volume overload. Please refer to Figure 1 which provides an evaluation/triage flowchart to make the determination of liver disease stage.

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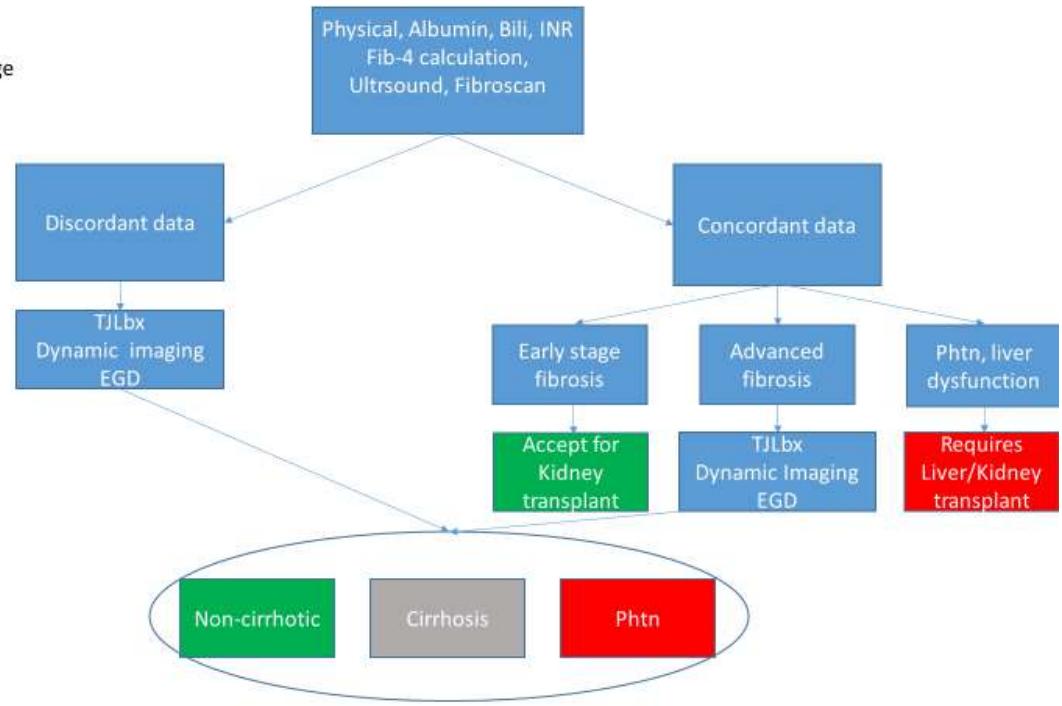
Figure 1:
Evaluation/Triage



Transplant triage

In the HCV interferon treatment era, when treatments were toxic and SVR poor, HCV viremic patients with any significant hepatic fibrosis (METAVIR stage 2 or greater) were generally excluded from kidney transplantation (19). This was on the basis of data that revealed an increase in graft loss and mortality amongst HCV viremic renal transplant recipients compared to HCV negative counterparts which was due in part to an increase in liver related outcomes but also cardiovascular events and infection. Risk of more rapid advancement of fibrosis in the setting of immune suppression, though not borne out in all serial biopsy studies, and fear of fibrosing cholestatic hepatitis which had been reported to occur at a frequency of 1.5% in older data by Munoz, impacted policy as well (21-28).

As HCV antiviral therapy was revolutionized and more recent data expanding acceptance criteria for kidney transplant were reported, it was necessary to re-evaluate and triage patients with co-morbid HCV and ESRD for transplantation. A new paradigm is now emerging. Patients with hepatic dysfunction and/or clinically significant portal hypertension remain more appropriately served by simultaneous liver/kidney transplantation owing to operative risk and potential for subsequent hepatic decompensation. Patients with early stage fibrosis may certainly be accepted for kidney transplant alone. It is also reasonable now to consider those with advanced fibrosis but clinically compensated disease to be accepted for kidney transplant alone. The precise divide is transplant center dependent.

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Timing of antiviral therapy

Timing of HCV therapy is primarily dependent upon the availability of an FDA approved DAA regimen and access to kidney allografts. Presently, of the 8 all oral FDA approved DAA regimens, three are labelled for use in patients with CrCl <30mL/min, as referenced in Table 3.

Table 3: Currently Available Direct Acting HCV Antiviral Regimens

Regimen	Manufacturer	Genotype coverage	Year of FDA approval	Labelled for ESRD	Data
Simeprevir/Sofosbuvir	Janssen Therapeutics/Gilead Sciences	1, 4	2014	No	
Sofosbuvir/Ledipasvir	Gilead Sciences	1, 4, 5, 6	2014	No	
Dasabuvir/Ombitasvir/Paritaprevir/ritonavir	AbbVie Inc	1, 4 w/o Dasabuvir	2014	Yes	RUBY 1&2
Daclatasvir/Sofosbuvir	Bristol-Myers Squibb/Gilead Sciences	1, 3	2015	No	
Grazoprevir/Elbasvir	Merck Pharmaceutical	1, 4	2016	Yes	C-SURFER
Sofosbuvir/Velpatasvir	Gilead Sciences	1, 2, 3, 4, 5, 6	2016	No	
Sofosvur/Velpatasivr/Voxilaprevir*	Gilead Sciences	1, 2, 3, 4, 5, 6	2017	No	
Glecaprevir/Pibrentasvir	AbbVie Inc	1, 2, 3, 4, 5, 6	2017	Yes	EXPEDITION-4
**this is considered a salvage regimen*					

Ombitasvir/paritaprevir/ritonavir/dasabuvir ("Viekira") and elbasvir/grazoprevir ("Zepatier") were first available with coverage limited to genotype 1 and 4 HCV. However both regimens contain a protease inhibitor which limits use in patients with advanced liver disease given an increased risk of hepatotoxicity for child turcotte pugh (CTP) B or C cirrhotics . RUBY 1 evaluated "Viekira" with ribavirin in G1a and without ribavirin in G1b patients for 12 weeks in G1 treatment naïve noncirrhotic patients (n=20) and reported SVR12 of 95%. Cohort 2 with cirrhotic patients is ongoing. RUBY reported at AASLD 2016 evaluated ribavirin free treatment of G1a or 4 patients with SVR12 of 100%. C-SURFER evaluated "Zepatier" for 12 weeks in a larger population (n = 224) of G1 treatment naïve and treatment experienced patients inclusive of compensated cirrhotics and revealed SVR12 of 99%.

Most recently (Aug 3, 2017) Abbvie's glecaprevir (2nd generation NS3/4a protease inhibitor) and pibrentasvir (NS5A replication complex inhibitor) co-formulated and marketed as "Mavyret" was approved with indication for patients with CrCl <30mL/min and has propelled treatment forward for this population as it is "pan-genotypic". This regimen was studied in the EXPEDITION 4 trial in 104 G1-6 HCV patients (inclusive of cirrhotics and non-cirrhotics and both treatment-naïve and treatment-experienced patients) for 12 weeks and revealed 100% SVR12 in a modified intention to treat analysis (29). Though similar to "Zepatier" and "Viekira", "Mavyret" contains a protease inhibitor limiting use in decompensated liver disease.

The Achilles' heel for the other DAA regimens in this population, is the renal clearance of the active metabolite of sofosbuvir – GS331007 (29). Therefore, genotype 2, 3, 5, & 6 patients with ESRD and co-morbid decompensated liver disease,

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remain without an option for interferon free therapy within FDA guidance (3, 29-31).

Gilead early on began to look at reduced dose sofosbuvir and ribavirin in patients with advanced CKD and saw significantly reduced efficacy. Subsequently, they have modified their trial to evaluate sofosbuvir/ledipasvir ("Harvoni"), data from which have been delayed (29). Real world cohort data evaluating off- label use of sofosbuvir in ESRD patients has emerged and is available to guide off-label therapy if a risk/benefit assessment justifies use (32). Such a situation might be treatment of a GT2 or 3 patient whom has subclinical portal hypertension and may be accepted as kidney transplant candidate alone if viral eradication and improvement of portal hypertension can be achieved. The Hepatitis C Therapeutic Registry and Research Network "HCV-Target" reported on data from patients treated with sofosbuvir either in combination with pegylated interferon/ ribavirin, ribavirin, simeprevir/ribavirin, or simeprevir. SVR was high at 81-88% across regimens with groups with eGFR </=30 and 31-45. Though even when limited to ribavirin-free regimens eGFR <30 patients more frequently experienced anemia, acute renal insufficiency, renal or urinary symptoms, and adverse events overall (32).

Access to kidney allografts is dependent upon identifying a living kidney donor or demographic/clinical factors predictive of wait time to a deceased donor organ offer which include geography (UNOS transplant region), blood type, panel reactive antibody score, and accrued wait time (33). As of the 2014 revision of the UNOS kidney allocation policy, kidney waitlist time is calculated based on the start of renal replacement therapy or documentation of GFR <20 (34). There are active clinical trials that are attempting to decrease discard rates of HCV viremic deceased donors by transplanting kidneys into HCV negative individuals, followed by anti-viral treatment. However, kidneys from HCV viremic donors are still largely allocated to HCV viremic patients, who have a distinct waiting time advantage and typically receive a kidney much faster than the general ESRD population. Given the known association of dialysis vintage, mortality and post-transplant outcomes, this advantage needs careful consideration prior to initiating anti-viral treatment in HCV viremic patients waitlisted for kidney transplant (35).

Generally, patients who have a living donor available or anticipated short wait time to deceased donor transplantation benefit from early anti-viral therapy which provides the opportunity for viral eradication with arrested progression of liver disease and minimizes the post-transplant risk for graft dysfunction, infection, diabetes, and fibrosing cholestatic hepatitis (FCH) (36-38). Pre-transplant therapy also eliminates the need to consider drug/drug interactions with immune-suppression regimens. While those with anticipated prolonged wait times may see an advantage to acceptance of an allograft from a HCV viremic donor which may dramatically

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reduce wait times and thereby reduce mortality by eliminating excess cardiovascular and infectious risk associated with renal replacement therapy. A consensus conference was convened in January 2017 by the American Society of Transplantation (AST) to review and provide guidance on the use of grafts from HCV viremic donors in solid organ transplantation (38). Transplantation of grafts from HCV viremic donors into HCV viremic recipients is becoming widely accepted. Considerations are the potential for genotype seroconversion if the donor/recipient genotype are disparate, potential for transmission of "resistant virus", timing of post- transplant therapy, and drug/drug interactions both of which are of low concern at this point in time. Transplantation of grafts from HCV viremic donors to negative recipients is being explored currently in the setting of clinical protocols and is otherwise advised only in the setting of IRB protocol/approval.

Conclusion

The success of DAA's has fundamentally changed how patients with ESRD should be managed. Prior to the introduction of DAA's the focus was on attempts at HCV eradication through interferon-based regimens and determination of transplant candidacy, which was often determined by thresholds of hepatic fibrosis. Now the clinical paradigm has shifted and includes important considerations of liver disease status, but also includes considerations of the advantage of early transplant with an HCV viremic deceased donor. The balance tends to favor deferral of HCV treatment, early transplant with a graft from a HCV viremic donor and HCV eradication post-transplant. Although this pathway is advantageous for many patients, level of sensitization, patient age, geographical location and availability of HCV allografts all need to be considered to develop individual patient-centered treatment plan.

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