Facilitating Patient-Centered Decision Making Around the Timing of Direct-Acting Antivirals in Patients With Hepatitis C Virus and CKD

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Since 2013, direct-acting antiviral (DAA) drugs have revolutionized the treatment of chronic hepatitis C virus (HCV) infection by offering relatively brief, well-tolerated, and highly effective regimens. At the same time, the United States faces an unprecedented opioid epidemic. With the increase in injection drug use, there have been surges in both HCV infection prevalence and overdose deaths, leading to more HCV-positive deceased kidney donors.[1] Individuals with chronic kidney disease (CKD) often have to make the complex decision of whether to undergo early DAA treatment (ie, to reduce the kidney and liver morbidity associated with HCV infection) or to defer treatment in exchange for potentially shorter transplant wait-list times (ie, for an HCV-positive donor kidney). Additionally, the high costs associated with DAAs[2] and the high mortality rates associated with HCV infection on dialysis also need to be considered.[3,4] The decision around timing of HCV infection treatment in CKD is highly nuanced, requiring consideration of an individual patient's risk factors, anticipated transplant wait-time, and overarching goal of care.[5,6] Educating and engaging patients to take part in this decision is both an ambitious and important undertaking.

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Before the introduction of DAAs, antiviral regimens for HCV infection relied on interferon and ribavirin. These medications required long treatment courses (often >48 weeks) and were poorly tolerated due to side effects and toxicity, particularly in patients with underlying CKD.[7] Accordingly, sustained virologic response at 12 weeks following treatment was often not achieved.[8,9] In contrast, DAAs are well tolerated, with few side effects, shorter duration of treatment (typically 12 with a range of 8-24 weeks), and excellent effectiveness, exhibiting sustained virologic response rates at 12 weeks generally >95%.[9] Therefore, the Infectious Diseases Society of America and the American Association for the Study of Liver Disease now recommend HCV infection treatment for most patients, except those with extremely limited life expectancy that would not be expected to be improved by HCV treatment.[9]

Two DAA regimens have been approved for use in CKD stages 3 to 5, including dialysis populations: glecaprevir/pibrentasvir (pan-genotypic) and grazoprevir/elbasvir (for genotype 1 or 4). Both regimens are safe and effective, achieving sustained virologic response at 12 weeks in >97% of patients.[10,11]

In the general population, HCV virologic cure is associated with lower all-cause mortality and liver disease progression.[9] Post hoc analyses of trial data and observational evidence suggest that virologic cure of HCV infection with DAAs improves kidney outcomes (ie, proteinuria and estimated glomerular filtration rate) in many patients with CKD.[12-14] Further investigation with longer follow-up is needed to better understand the effect of DAA treatment on long-term kidney outcomes in patients with CKD, and to evaluate whether treatment reduces adverse outcomes in dialysis patients.[15] In individuals with HCV infection on the kidney transplant waitlist, willingness to accept an HCV-positive donor kidney can greatly reduce the time they wait to receive a kidney transplant.[16,17] However, HCV infection in kidney transplant recipients is associated with increased mortality and earlier allograft loss compared with HCV-negative recipients.[4]

In a retrospective study of 442,171 dialysis patients, including 31,624 HCV-positive patients, we found that HCV-positive dialysis patients had a slightly higher mortality risk (adjusted hazard ratio, 1.09; 95% confidence interval [CI], 1.07-1.11) and a substantially lower likelihood of being waitlisted for a kidney transplant (subdistribution hazard ratio, 0.67; 95% CI, 0.61-0.74) compared with HCV-negative dialysis patients.[18] At 2 years posttransplantation, HCV-positive dialysis patients experienced survival benefit from receiving an HCV-positive donor kidney compared to remaining on the waitlist. Given that HCV infection can now be successfully treated with DAAs after kidney transplantation,[19] there is an opportunity for patients to potentially benefit from shorter waitlist times by accepting HCV-positive donor kidneys and treating their HCV infection after transplantation.[20] Nonetheless, the benefits of deferring DAA therapy until after HCV-positive donor kidney transplantation must be weighed against the risks for liver decompensation while awaiting transplantation.[5] Additionally, because there is growing enthusiasm in the transplantation community for the use of HCV-viremic donors in HCV-negative recipients,[21,22] the wait-time advantage associated with HCV-positive donors may not be preserved in the future.

In this issue of *Kidney Medicine*, George et al[23] present results of a pilot study evaluating the feasibility and utility of a tool for educating patients with CKD and HCV infection about the timing of DAA therapy. The study used a pre-post exposure design to assess participants' improvement in decision self-efficacy, conflict, and knowledge after using the patient education and decision

support tool. The authors selected a study population that was generalizable to many patients seen in urban medical centers with stages 3 to 5 CKD and HCV infection, including relatively high proportions of non-Hispanic black patients, patients with low income, and patients with limited health literacy. The tool demonstrated reasonable response (79.5%) and completion (80.0%) rates and fair participant usability (usability score, 69.86 ± 20.43 of a maximum of 100). Additionally, the tool yielded a modest but significant improvement in knowledge (mean difference, 12.3% of questions answered correctly before vs after exposure to the tool; $P < 0.001$) and confidence about participants' choice (mean difference of 0.47 decisional conflict score; $P = 0.05$), but not decision self-efficacy (mean difference of 2%; $P = 0.48$). These results are promising, opening a door to better empowering patients to make decisions about the timing of DAA therapy in the future.

Of note, the vast majority of participants selected a paper version rather than the intended electronic version of the tool, stressing the importance of ensuring that such tools are widely accessible to patients and that they do not necessarily require technological competence to be used. An important limitation was the minimal evidence-based literature on the optimal timing of DAA therapy from which to sculpt the decision tool at the time of its inception, which may benefit from updating with more recent pertinent findings.[5,12,13]

Our previous findings[4,5,16-19,24] underscore the importance of greater engagement with HCV-positive patients to encourage them to undergo kidney transplantation evaluation while deeply considering the timing of DAA therapy around that decision. When considering subtle distinctions across the results of largescale research studies, we often lose insight into the challenges of delivering information about such important but complicated details to individual patients. Given the particular complexity of decision making around the timing of DAA therapy in individuals with CKD and HCV infection, the development of a patient education tool is timely and important. To be able to make a well-informed decision about the timing of DAA therapy, patients require far more counseling and education than is available in a typical clinician visit. George et al's patient-centered approach to this complex medical decision takes a very important step in the right direction.

ARTICLE INFORMATION

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