



## New Treatment Options for Hepatitis C Virus Infection in End-Stage Kidney Disease: To Treat or Not to Treat

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**H**epatitis C virus (HCV) infection is highly prevalent among individuals with chronic kidney disease (CKD) and is associated with worse health outcomes, including more rapid progression to end-stage kidney disease, higher mortality on dialysis therapy, and among those receiving a kidney transplant, increased risk for posttransplantation diabetes and decreased patient and allograft survival.

*Commentary on Gane E, Lawitz E, Pugatch D, et al. Glecapravir and pibrentasvir in patients with HCV and severe renal impairment. N Engl J Med. 2017;377(15):1448-1455.*

Before the introduction of highly effective direct-acting antivirals in 2013, prolonged therapy with interferon and ribavirin was standard of care, and eradication of HCV was rare in patients with end-stage kidney disease. Although interferon and ribavirin are poorly tolerated in patients with advanced CKD or end-stage kidney disease, pretransplantation treatment was strongly recommended due to the unacceptably high risk for acute rejection and allograft dysfunction in kidney transplant recipients treated with interferon in the posttransplantation setting.<sup>1-3</sup> The availability of highly effective direct-acting antivirals that can be used in the setting of advanced CKD has changed clinical practice, with many transplantation centers now postponing HCV therapy to allow the use of HCV-positive donor organs in HCV-positive recipients.

First-generation direct-acting antivirals had only a modest impact on treatment duration and rates of sustained virologic response (SVR) or cure when used in combination with interferon, and many clinicians deferred therapy in stable patients in anticipation of more effective second-generation agents. Second-generation direct-acting antivirals have dramatically increased the rates of SVR with a shorter duration of therapy, fewer adverse events, and without interferon. In late 2015, the randomized controlled C-SURFER trial demonstrated the efficacy and safety of combination therapy with the direct-acting antivirals grazoprevir and elbasvir for the treatment of HCV genotype 1 infection in individuals with stages 4 to 5 CKD or end-stage kidney disease; coformulated elbasvir-grazoprevir is also approved for the treatment of genotype 4 infection based on studies of individuals without CKD.<sup>4,5</sup> The fixed-dose combination of ombitasvir, paritaprevir, and ritonavir does not require dose reduction for decreased glomerular filtration rate (GFR) and is also approved for the treatment of HCV genotype 1 (in combination with dasabuvir) and genotype 4 infection in patients with CKD.<sup>6,7</sup>

Despite these advances, treatment gaps remained. Although genotypes 1 and 4 are the most common HCV genotypes in the United States and Africa, respectively, a significant minority of patients have advanced CKD and HCV genotype 2, 3, 5, or 6 infection. These patients have limited treatment options. There are additional treatment concerns for transplant recipients or patients with glomerular disease maintained on treatment with calcineurin inhibitors (CNIs). Coadministration of elbasvir-grazoprevir with cyclosporine is contraindicated, and close monitoring is recommended during coadministration with tacrolimus, although elevations in tacrolimus concentrations are generally modest.<sup>5</sup> The ritonavir-boosted ombitasvir-paritaprevir regimen also has potential drug-drug interactions with CNIs.<sup>6,7</sup>

### What Does This Important Study Show?

In a recent issue of the *New England Journal of Medicine*, Gane et al<sup>8</sup> report the results of EXPEDITION-4, a phase 3 open-label trial evaluating the efficacy and safety of the pangenotypic direct-acting antivirals glecapravir and pibrentasvir for use in the CKD and end-stage kidney disease population. EXPEDITION-4 enrolled 104 adults with HCV genotypes 1 to 6 infection and estimated GFRs < 30 mL/min/1.73 m<sup>2</sup>, including 85 patients receiving maintenance hemodialysis. Participants had compensated liver disease and were HCV treatment naive (58%) or for whom interferon- or sofosbuvir-based therapy had failed (42%); patients for whom any other direct-acting antiviral therapy had previously failed, as well as those who were treatment experienced with genotype 3 infection, were excluded. Three-quarters of enrolled participants were men and 62% were white, with a median age of 57 years.

All participants received daily glecapravir, 300 mg, and pibrentasvir, 120 mg, in coformulated tablets, and 99 of the 104 (95%) participants completed 12 weeks of therapy. The primary end point of SVR at week 12 was achieved in 102 (98%) participants, including 3 who had discontinued the study drug between weeks 8 and 12 because of adverse events. A fourth participant who discontinued at week 4 had a detectable HCV viral load at week 12, and there was 1 unrelated death at week 2. Among the 102 participants with an SVR at week 12, a total of 100 had a documented SVR at week 24 and 2 were lost to follow-up. Overall, adverse events occurred in 71% of participants, with the most common events reported being pruritis, nausea, and fatigue, symptoms commonly observed in patients with advanced CKD. No serious adverse events were considered related to the study drug.<sup>8</sup>

These results support the efficacy and safety of glecapravir-pibrentasvir as an alternative to elbasvir-grazoprevir for the treatment of HCV infection in patients with advanced CKD or end-stage kidney disease. Limitations of the study included the open-label design and questions of generalizability; there were few women and participants of nonwhite race and very small absolute numbers of participants with genotype 5 or 6 infection. However, overall SVR rates were similar to those in the non-CKD population, and the safety profile appears to be acceptable.

### How Does This Study Compare With Prior Studies?

The growing availability of effective and reasonably well-tolerated direct-acting antiviral regimens that can eradicate HCV infection regardless of kidney function has raised the clinical question of who and when to treat. Observational studies have supported the efficacy and safety of direct-acting antivirals in liver and kidney transplant recipients,<sup>9,10</sup> so the ability to eradicate HCV after transplantation is not in question. Unique challenges in the treatment of HCV infection following kidney transplantation include labile kidney function, which can prohibit the use of sofosbuvir-based regimens, and drug-drug interactions between some direct-acting antivirals and the CNIs. Like elbasvir-grazoprevir, glecapravir-pibrentasvir should be avoided in patients maintained on cyclosporine treatment, but there are no observed drug-drug interactions with tacrolimus.<sup>11</sup> For patients with genotype 1 or 4 infection and GFRs < 30 mL/min/1.73 m<sup>2</sup>, either elbasvir-grazoprevir or glecapravir-pibrentasvir would be acceptable, whereas glecapravir-pibrentasvir is preferred in patients with genotypes 2, 3, 5, or 6.

Because the waiting time for HCV-positive deceased donor kidneys is substantially shorter in many geographic regions,<sup>12</sup> transplantation centers often recommend deferring HCV treatment in stable kidney transplantation candidates without significant liver fibrosis to facilitate earlier transplantation with HCV-positive organs. Although this approach was adopted without evidence from randomized controlled trials, it has rapidly become the standard of care in many urban transplantation centers, where patients face long waiting times on dialysis therapy. More recently, the American Society of Transplantation convened a multidisciplinary panel to consider the implications of offering HCV-positive organs to HCV-negative recipients.<sup>13</sup> A single-center pilot study demonstrated excellent short-term outcomes in 10 HCV-negative kidney transplant recipients who consented to accept a high-quality organ from a donor with HCV genotype 1 infection.<sup>14</sup> All participants seroconverted following transplantation, with SVRs achieved in 100% after 12 weeks of elbasvir-grazoprevir treatment. Although genotyping was performed on all donor organs before transplantation in the pilot study, the availability of a pangenotypic direct-acting antiviral regimen that does not require renal dose reduction may eliminate the need for rapid pretransplantation genotyping, with the associated costs, potential delays, and discard of organs from non-genotype 1- or 4-infected donors. Although the future of this

approach is uncertain and it is still considered experimental, expanding the HCV-positive donor pool to include all recipients would largely eliminate the current waiting time advantage for HCV-positive transplantation candidates.<sup>15</sup>

### What Are the Implications for Nephrologists?

For now, we and many others recommend postponing HCV treatment until after transplantation to facilitate the use of HCV-positive donor organs in HCV-positive recipients. There are situations in which this recommendation may not apply, including for transplantation candidates with an approved living donor or those with favorable blood groups or in areas with short wait times. Patients with advanced liver disease at risk for decompensation, patients with long dialysis vintage (and by extension long accumulated waiting time), and patients with human immunodeficiency virus (HIV)-HCV coinfection (who are at risk for rapid progression to cirrhosis) may also benefit from consideration of treatment while on dialysis therapy. Additionally, it is important to include the patient perspective in making treatment timing decisions and acknowledge the social stigma associated with HCV infection. If in the future the use of HCV-positive donor organs for HCV-negative recipients is broadly adopted, HCV-positive transplantation candidates would lose their wait-time advantage. In that scenario, we would suggest treatment while on the waiting list to reduce the risk for progressive liver disease and extrahepatic manifestations.

The optimal timing for HCV therapy is a dynamic aspect of the field, with shifting recommendations depending on available treatment characteristics and organ allocation practices. The expanding options for treatment of HCV infection in patients with advanced CKD and end-stage kidney disease is of benefit to all patients regardless of their transplantation candidacy.

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