Hep C Treatment Options for Those With Chronic Kidney Disease Are Looking Up

A promising new regimen that will address unmet needs for this population is poised for FDA approval.

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These are golden times for people with hepatitis C virus (HCV). Since Gilead Sciences' blockbuster direct-acting antiviral (DAA) Sovaldi (sofosbuvir) hit the market in late 2013, an increasingly broad crop of other hep C drugs have been approved, rendering curing HCV relatively easy and quite safe for a swath of the hep C population.

This all stands in stark contrast to the recent past, when attempting to cure hep C required braving months of interferon and ribavirin, a treatment made onerous by its severe side effects—anemia, depression and flu-like symptoms—that wasn't even very effective at curing the virus.

Treatment advances notwithstanding, today there remain key subgroups of those living with hep C who still have unmet DAA treatment needs. One such subgroup is people with chronic kidney disease (CKD), who likely need hep C treatment urgently. Unfortunately, their compromised health can make hep C treatment challenging, especially since Sovaldi, still the cornerstone of DAA treatment, is excreted through the kidneys and therefore not recommended for those with stage 4 or 5 CKD. This also applies to Gilead's Harvoni (ledipasvir/sofosbuvir), Epclusa (sofosbuvir/velpatasvir) and Vosevi (sofosbuvir/velpatasvir/voxilaprevir) combination pills, all of which contain sofosbuvir.

There are indeed available DAA treatments for people with CKD—for example, the Viekira regimen (ombitasvir/paritaprevir/ritonavir and dasabuvir)—but they are approved only for those with genotypes 1 or 4 of the virus. In other words, these treatments are not pangenotypic—a term that refers to DAA regimens that treat all six major HCV genotypes—and don't provide approved options for those with CKD and genotypes 2, 3, 5 or 6.

"There have been advances in treatment of hepatitis C, particularly now in special populations," says K. Rajender Reddy, MD, director of hepatology at the Perelman School of Medicine at the University of Pennsylvania. "We can treat those with chronic kidney disease with the hope and

expectation of the stability of their kidney disease and in some cases an improvement. While the current regimens are effective, they're not pangenotypic. And we expect to see pangenotypic regimens evolve down the road. So we've come a long way since the days of interferon and ribavirin."

Reddy is the coauthor of a review of the available research on hep C treatment for people with CKD, published in January in the Journal of Viral Hepatology. The paper provides a detailed look at what we do and do not know about hep C and its treatment for this population, as well as what we can hope to gain from upcoming advances in DAA therapy.

CKD, which for the purpose of Reddy's review includes people with stage 4 or 5 of the condition, refers to those who are on dialysis or who have an estimated glomerular filtration rate (eGFR) at or below 30 millimeters per minute per 1.73 meters squared. Those with an eGFR between 15 and 29 mL/min have stage 4 (severe) CKD, while those with an eGFR below 15 mL/min have stage 5 CKD, also known as end-stage kidney disease.

According to Reddy's review, research has firmly established that people with hepatitis C are more likely to develop CKD, even if they don't have any additional risk factors for kidney problems, such as diabetes or high blood pressure. Specifically, researchers estimate that having HCV is associated with a 23 percent higher risk of CKD compared with being HCV negative. Additionally, a scientific analysis that looked at more than 150,000 U.S. veterans found that having hep C more than doubles the risk of developing end-stage kidney disease.

Living with hep C for a greater period of time also apparently contributes to the risk of developing CKD. As the virus fuels severe liver disease and other health conditions in many people, these health problems can in turn spur kidney damage.

Hep C also accelerates existing kidney damage and worsens health prospects among those who do have CKD. There's also the finding that, because of end-stage kidney disease, individuals on dialysis have a greater risk of death if they have HCV. Additionally, the virus lowers the likelihood of graft survival among those receiving a kidney transplant. What's more, scientists are finding increasing evidence that HCV likely raises the risk of sickness and death after receiving a kidney transplant.

Unfortunately, according to Reddy, there are no available data showing how curing hep C may improve health prospects for those with kidney disease. "Intuitively, we think that it would," he says.

Scientific uncertainty about hep C treatment's benefits for this population aside, experts advise that all people with impaired kidney function consider DAA treatment to reduce their risk of liver disease progression as well as sickness and death related to kidney disease. The need for HCV treatment is especially great if an individual has received a kidney transplant. Also, hep C treatment guidelines recommend that those on dialysis be prioritized for treatment. (Some insurers may limit who may receive coverage for the highly expensive DAA treatments, prioritizing those with more advanced liver disease or who have other conditions like HIV.)

Treatment options: A new regimen is poised to help people with

In early August, the Food and Drug Administration (FDA) is scheduled to issue a decision on whether to approve AbbVie's DAA regimen Maviret (glecaprevir/pibrentasvir, formerly known as G/P). If approved, Maviret will finally provide a proven treatment option for people with all six HCV genotypes who have CKD.

"If G/P becomes approved it will be an advancement over what we have in treating hepatitis C in the kidney disease population," Reddy says.

Research on Maviret indicates that negligible amounts of the drugs included in the regimen are excreted through the kidneys. So people with end-stage kidney disease won't need to adjust its dose for safety reasons.

A recent Phase III trial of Maviret included 104 people with CKD, including those who had and had not been treated for hep C before and those with and without compensated cirrhosis (the milder form of the severe liver disease). The proportion with each HCV genotype was as follows: genotype 1 (50 percent), genotype 2 (16 percent), genotype 3 (11 percent), genotype 4 (19 percent) and genotypes 5 and 6 (2 percent).

After 12 weeks of treatment, 98 percent of the participants were cured, with very few serious adverse health events seen during treatment.

This trial led researchers to conclude that Maviret is safe and effective in individuals who have severe impairment of the kidneys or are on dialysis.

Other treatment options

People with an eGFR below 30 mL/min are advised against taking sofosbuvir-containing regimens. As mentioned previously, the drug is included in Harvoni, Epclusa and Vosevi. Sovaldi, sofosbuvir's brand name, can also be paired with AbbVie's Daklinza (daclatasvir) or Janssen's Olysio (simeprevir).

Additionally, while ribavirin is still sometimes paired with DAA regimens to improve their effectiveness, giving the drug to those whose CKD is a concern because they may have an impaired ability to eliminate it through their kidneys. Dialysis may also not be able to clear the drug properly. Some people with genotype 1a in particular may require ribavirin to improve their chances of achieving an HCV cure.

Despite these major impediments, many people with CKD have managed to beat hepatitis C with today's available drugs.

The Phase III C-SURFER trial tested Merck's Zepatier (grazoprevir/elbasvir) among 235 people with HCV genotype 1 and CKD, a majority of whom were on dialysis. After 12 weeks of treatment, 94 percent of them were cured, with only five individuals stopping treatment because of adverse

health events.

A Phase III study of Viekira, called RUBY-I, gave the regimen to 20 people with CKD who had genotype 1 of HCV, did not have cirrhosis and were first-timers to hep C treatment. The 13 people with genotype 1a were given 200 mg of ribavirin once daily to boost the regimen's efficacy; unfortunately, they tolerated the drug poorly. Nevertheless, 90 percent of the overall group was cured after everyone completed 12 weeks of treatment.

In other studies of Viekira among people with CKD that included those with cirrhosis and those who had been previously treated for HCV, cure rates were in the mid-90 percent range. The findings of one trial suggested that ribavirin might not even be necessary for those with genotype 1a and CKD who take Viekira, although further research is needed.

Braving sofosbuvir-based treatment

The recommendations against giving sofosbuvir-based regimens to those with CKD notwithstanding, Reddy concluded in his review that such treatments are indeed still a possibility for those with end-stage kidney disease. His paper stresses that "[c]areful assessment and monitoring of patients with severe renal [kidney] impairment undergoing sofosbuvir therapy is crucial, especially in patients with advanced cirrhosis."

Various studies of sofosbuvir-based regimens have in fact included people with CKD, showing cure rates ranging between 87 to 100 percent among this demographic.

The recent HCV-TARGET study, a long-term real-world study of individuals receiving DAA treatment, provided much-needed evidence about the safety and efficacy of sofosbuvir-based regimens among those with CKD. Within this cohort of individuals there were 73 people with eGFR at or below 45 mL/min, including 18 with CKD stage 4 or 5. (Those with an eGFR between 30 and 44 mL/min have moderate CKD, or stage 3B.) All of them received the full 400 mg per day dose of Sovaldi. There was no significant difference in cure rates based on whether individuals had an eGFR greater than or below 45.

However, those with eGFR of 45 or below experienced greater anemia-related adverse health events and worsening kidney function during HCV treatment with sofosbuvir-based regimens.

After adjusting the data for various factors, the study authors found that having an eGFR at or below 45 when starting DAA treatment was the only factor that predicted worsening kidney function among the study participants.

As the Journal of Viral Hepatology review points out, various factors may have dragged down kidney function in this group regardless of whether they took DAAs. For example, 57 percent had received a kidney or liver transplant, 64 percent had cirrhosis and 44 percent had diabetes—factors that can all accelerate kidney damage.

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