LETTER TO THE EDITOR

Full-dose sofosbuvir and daclatasvir for chronic hepatitis C infection in haemodialysis patients

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To the Editor,

The registration of sofosbuvir-containing regimens has changed the treatment of hepatitis C virus (HCV) infection dramatically by achieving high sustained virological responses (SVR).[1-3] Even previously difficult-to-treat patients can now be treated safely by interferon-free therapies, resulting in potential reduction of HCV disease burden in the Netherlands.[4-5] However, treating patients with end-stage renal disease (ESRD) remains difficult. Currently approved options for ESRD patients still contain (pegylated) interferon as a backbone, which is historically associated with low SVR rates and high side effect profiles.[6-8] Since HCV infection negatively impacts morbidity and mortality compared with non-HCV dialysis patients, effective treatment is especially pivotal for this patient group.[9] In addition, clearance of HCV will increase the chance of getting a renal transplant, as HCV-infected individuals demonstrate higher mortality, graft loss rate and episodes of rejection after renal transplantation.[10] Therefore, there is a clear need to treat haemodialysis patients with interferon-free therapies.

The recommended dose of 400 mg sofosbuvir in patients without renal insufficiency is not approved for patients on haemodialysis owing to concerns of accumulating metabolites with potential cardiovascular and hepatobiliary toxicity.[11] Indeed, sofosbuvir is metabolised to the active metabolite GS461203 which works intracellularly, and subsequently to the inactive metabolite GS331007, which is the predominant metabolite in plasma.[12] Because GS331007 is eliminated by the kidney, concern was raised that especially this metabolite would accumulate in patients on haemodialysis, potentially leading to toxicity.[13] Lowering the dose is not a desirable option, as sofosbuvir is a prodrug and potentially could lead to lower levels of the active metabolite GS461203 and lower efficacy. Indeed, a small study in ten genotype 1 HCV infected patients with a creatinine clearance < 30 ml/min using sofosbuvir 200 mg daily showed low efficacy (SVR 40%).[14] These findings suggest that standard doses of sofosbuvir 400 mg might be necessary to achieve SVR in haemodialysis patients, but the tolerability is unknown.

We treated two HCV genotype 1 patients with standard dose sofosbuvir (400 mg) and daclatasvir (60 mg) once daily for 12 weeks. Both patients were on haemodialysis at the start of anti-viral treatment. The aetiology of ESRD was reflux nephropathy and diabetic nephropathy for patient A and B respectively.

Patient A (male, 54 years) had treatment-naïve chronic HCV genotype 1b with Child-Pugh A cirrhosis, and started with a regimen consisting of sofosbuvir/daclatasvir/ribavirin. Ribavirin was dosed at 200 mg daily after an initial loading dose of 1200 mg for the first two days, and was subsequently adjusted based on weekly measured ribavirin levels. The pre-treatment HCV RNA level was 72,000 IU/ml, dropped to undetectable at week 4, and remained undetectable until 12 weeks after treatment (SVR). Due to persistent anaemia after lowering the ribavirin dose, the ribavirin was stopped at week 5. No other adverse events occurred. One of the reasons that patient A refused a transplant (after already having two renal transplant rejections) was fear of HCV. After successful treatment, he is now reconsidering transplantation.

Patient B (female, 63 years), who had chronic HCV genotype 1a with Child-Pugh A cirrhosis, had previously relapsed on pegylated interferon and ribavirin therapy. She was treated for 12 weeks with standard dose sofosbuvir/daclatasvir; ribavirin was withheld due to previous side effects. The HVC RNA level dropped from 488,000 IU/ml pre-treatment to undetectable after four weeks of treatment, and remained undetectable 12 weeks post-treatment. No adverse events occurred in this treatment period. Of note, the pre-existent anaemia

improved after finishing therapy. She is now in the screening process for receiving a renal transplantation.

Both patients achieved SVR12 after receiving full-dose sofosbuvir, and tolerated treatment well. We did not observe any evidence of hepatobiliary (1.5 fold elevation of aminotransferase or alkaline phosphatase level) or cardiovascular toxicity (occurrence of myocardial infarction/angina/arrhythmia) during treatment. Only patient A reported anaemia, which resolved after cessation of ribavirin.

We are the first to report that the interferon-free sofosbuvir-based regimen including daclatasvir is effective and tolerated well in cirrhotic HCV genotype 1 patients on haemodialysis. Our results are in line with three recent case series that investigated other sofosbuvir-containing regimens in HCV genotype 1 patients with ESRD.[12,15,16] All three case series used 400 mg sofosbuvir with simeprevir or ledipasvir and reported good safety profiles and superior SVR when compared with SVR's (< 60%) of interferon-based therapies.[6,7,17] Moreover, most studies used a ribavirin-free regimen. Given the risk of worsening of pre-existent anaemia when using ribavirin (see patient A) and the superior SVR observed in aforementioned trials, the use of sofosbuvir without ribavirin would be a viable option in this specific population. On the other hand, European Association for the Study of the Liver (EASL) guidelines recommend the use of ribavirin in patients with cirrhosis, where possible. The low number of patients in this and other studies remains a limiting factor for definite conclusions. When ribavirin is used, we recommend therapeutic drug monitoring to prevent concentration-related anaemia by overdosing of ribavirin in this group of HCV patients with renal impairment.

The Dutch HCV guideline committee (http://www.richtsnoer.nl/index.html) advises to use full-dose sofosbuvir in HCV patients with ESRD (if treatment is warranted), as lowering the dose increases the chance for virological failure more than the risk for toxicity when using a standard dose. The low side effect profiles mentioned in our letter and observed in recent studies support this statement.

Previous studies showed that only 18% of GS331007 is removed by a four-hour haemodialysis session, indicating that these patients are exposed to higher levels of this inactive metabolite compared with subjects with normal renal function.[11,18] Given the low side effect profiles reported in the aforementioned studies, and the fact that the cardiovascular and hepatobiliary toxicity was only observed in premarket animal studies, it remains the question whether this metabolite is really toxic for ESRD patients for the duration of 12-24 weeks of treatment. Unfortunately, we did not measure levels of sofosbuvir or GS331007 in these two patients. Further pharmacokinetic/dynamic studies are necessary to unravel the potential toxicity of sofosbuvir and its metabolites in patients with ESRD.

The use of sofosbuvir-containing regimens in haemodialysis patients may be short-lived. New regimens that are completely metabolised by the liver are close at hand. The combination of grazoprevir combined with elbasvir for HCV genotype 1 infected patients with ESRD has recently been approved by the US Food and Drug Administration (FDA), as well as the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir, given the excellent preliminary results.[19,20] However, these combinations will be contraindicated in patients with Child-Pugh C (grazoprevir) or decompensated Child-Pugh B/C cirrhosis (ombitasvir/paritaprevir/ritonavir). Since a large proportion of patients with advanced cirrhosis will have ESRD, sofosbuvir-containing regimens remain a relevant therapeutic option for HCV patients on haemodialysis.

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