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SCIENTIFIC LETTERS

Sofosbuvir antiviral therapy in HCV patients with severe renal failure☆

Tratamiento antiviral con sofosbuvir en pacientes con hepatitis C e insuficiencia renal severa

Modern antiviral drugs for the treatment of chronic hepatitis C achieve high cure rates; however, treatment of patients with chronic kidney disease (CKD) is still challenging due to the lack of efficacy and safety data in this patient population.[1]

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for HCV replication. It is a nucleotide prodrug, whose main (>90%) metabolite is GS-331007.[2] Relative to patients with normal renal function, the area under the curve for sofosbuvir and GS-331007, which is eliminated through the kidney, is 171% and 451% higher, respectively in patients with severe CKD.[1,2]

We present data from 4 patients with severe CKD and hepatitis C who were treated in our department with different antiviral regimens containing sofosbuvir (Tables 1 and 2). The first 2 were treated for severe CKD with creatinine clearance (CrCl) of less than 30 ml/min. One of them was in a peritoneal haemodialysis program and on a hepatorenal transplant waiting list, the other presented CKD associated with cryoglobulinaemia. These 2 patients had presented hydropic decompensation and were on diuretic therapy. They were treated off label with sofosbuvir + daclatasvir for 24 weeks, with resolution of ascites and clinical improvement. The third patient presented CKD with CrCl 30 ml/min and received 12 weeks of treatment with simeprevir + sofosbuvir. Creatinine was elevated during treatment but had improved considerably by the end. The last patient presented CKD due to diabetic nephropathy with CrCl 33 ml/min, and received 12 weeks of treatment with sofosbuvir + ledipasvir. Creatinine was elevated during treatment but had almost returned to baseline levels by the end. Treatment was well tolerated by all patients, with no significant adverse effects. None of the patients received ribavirin, and all 4 achieved a sustained viral response at week 12 and 24 post treatment.

New oral antiviral drugs against hepatitis C achieve a high cure rate and have few side effects. Nevertheless, the most appropriate treatment has yet to be evaluated in some patient populations, such as those with severe CKD and CrCl <30 ml/min. In these patients, current guidelines[3,4] still recommend pegylated interferon with low-dose ribavirin in genotype 2, 3, 5 or 6. Triple therapy with dasabuvir + paritaprevir/ombitasvir/ritonavir is recommended in genotype 1 and 4. However, a high interaction rate coupled with the polypharmacy typical of patients with end-stage renal disease often make this impractical. Other therapies recommended in these patients are simeprevir and daclatasvir. These can be administered in combination in select patient groups, although this is not described in current guidelines. In the near future, the combination of grazoprevir/elbasvir may be the regimen of choice in these patients, since it has shown high rates of efficacy in patients with CKD.[1,5]

Sofosbuvir is a pan-genotypic NS5B polymerase inhibitor in which the primary metabolite GS-331007 is eliminated through the kidneys.[1,2] Serum levels of GS-331007 increase significantly in patients with CKD. Although there is so far no evidence of toxicity associated with this metabolite, sofosbuvir is not recommended in patients with CrCl below 30 ml/min.[1–4]

Few case series of patients with severe CKD treated with sofosbuvir have been published. A series of patients with severe CKD treated with 200 mg of sofosbuvir plus ribavirin daily was presented at the AASLD-2014 conference. Although the therapy was well tolerated, sustained response was poor. This dosage is considered suboptimal and is not recommended.[6] The following year, in the AASLD-2015 conference, small series of CKD patients with CrCl <30 ml/min treated with combinations of antiviral drugs, including sofosbuvir 400 mg/day were presented. No cases of impaired kidney function were reported, the drug was associated with high cure rates and was well tolerated by all patients.[7–9]

We also found the therapy to be well tolerated, with no adverse effects and rapid patient-reported improvement in all cases. Although creatinine levels were slightly elevated during treatment, no dosage changes were required, and post-treatment creatinine levels improved over baseline levels in 3 out of 4 patients.

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Table 1 Patient characteristics.

	Sex/age	Genotype/load	Grade of fibrosis	Previous treatment	Current treatment	RVR	SVR 12
Patient 1	Male 54 years	1a 1,714,067 IU/ml	F4	*Naive*	SOF + DCL24 weeks	Yes	Yes
Patient 2	Female 70 years	3a 257,000 IU/ml	F4	*Null-responder* INF + RBV	SOF + DCL24 weeks	Yes	Yes
Patient 3	Female 78 years	1b 191,649 IU/ml	F4	*Null-responder* INF + RBV	SOF + SIM12 weeks	No	Yes
Patient 4	Male 62 years	1b 508,122 IU/ml	F3	Relapsing INF + RBV	SOF + LDV12 weeks	Yes	Yes

DCL: daclatasvir 60 mg/day; INF: interferon; LDV: ledipasvir 90 mg/day; RBV: ribavirin; RVR: rapid viral response at week 4 of treatment; SIM: simeprevir 150 mg/day; SOF: sofosbuvir 400 mg/day; SVR 12: sustained viral response at week 12 after treatment.

Table 2 Creatinine and creatinine clearance during therapy.

	Baseline	Week 2	Week 4	Week 8	Week 12	Week 24	SVR 12
Patient 1	Cr: 3.16 CrCl: 23.97	Cr: 4.17 CrCl: 15.04	Cr: 3.44 CrCl: 18.76	Cr: 3.61 CrCl: 17.77	Cr: 3.58 CrCl: 17.94	Cr: 3.42 CrCl: 18.91	Cr: 2.47 CrCl: 27.53
Patient 2	Cr: 2.41 CrCl: 19.8	Cr: 2.56 CrCl: 18.53	Cr: 2.34 CrCl: 20.55	Cr: 2.47 CrCl: 19.31	Cr: 2.6 CrCl: 18.2	Cr: 2.4 CrCl: 19.96	Cr: 1.96 CrCl: 25.21
Patient 3	Cr: 1.63 CrCl: 30	Cr: 1.87 CrCl: 26.04	Cr: 1.62 CrCl: 30.73	Cr: 1.5 CrCl: 33.58	Cr: 1.63 CrCl: 30.51	–	Cr: 1.15 CrCl: 45.64
Patient 4	Cr: 2.06 CrCl: 33.3	Cr: 2.51 CrCl: 26.09	Cr: 2.23 CrCl: 29.91	Cr: 2.41 CrCl: 26.34	Cr: 2.58 CrCl: 25.28	–	Cr: 2.37 CrCl: 28.1

Cr: creatinine (mg/dl); CrCl: creatinine clearance (ml/min).

We present efficacy and safety findings in a small series of patients with CKD treated with sofosbuvir. Although prospective studies are no doubt needed, we believe that the benefit of this therapy should be evaluated on a patient-by-patient basis.

References

1. Maruyama A, Partovi N, Yoshida EM, Erb SR, Azalgara VM, Hussaini T. A review of direct-acting antivirals for the treatment of hepatitis C in patients with advanced chronic kidney disease. Nephrol Dial Transplant. 2015, pii:gfv361 [Epub ahead of print].
2. Sovaldi®. Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf [accessed 19.11.15].
3. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. Unique patient populations: patients with renal impairment; 2015. Available from: http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-renal-impairment [accessed 07.08.15].
4. European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol. 2015;63:199–236.
5. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour H Jr, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386:1537–45.
6. Edward JG, Richard AR, Maurizio B, Benedict M, Lin L, Karim S, et al. Safety, anti-viral efficacy and pharmacokinetics (PK) of sofosbuvir (SOF) in patients with severe renal impairment. Hepatology. 2014;60 Suppl. 1:667A.
7. Martin P, Gane EJ, Ortiz-Lasanta G, Liu L, Sajwani S, Kirby B, et al. Safety and efficacy of treatment with daily sofosbuvir 400 mg + ribavirin 200 mg for 24 weeks in genotype 1 or 3 HCV-infected patients with severe renal impairment. Hepatology. 2015;62 Suppl. 1:765A.
8. Dumortier J, Bailly F, Pageaux GP, Vallet-Pichard A, Radenne S, Habersetzer F, et al. Sofosbuvir-based antiviral therapy in HCV patients with severe renal failure. Hepatology. 2015;62 Suppl. 1:781A.
9. Kitzman G, Davis E, Monico J, Arendale E, Borg BB. Sofosbuvir is well tolerated and effective in chronic hepatitis C patients with advanced renal disease and/or on hemodialysis. Hepatology. 2015;62 Suppl. 1:792A.

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