PERSPECTIVE

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A new era in the treatment of hepatitis C infection in uraemic patients: are we nearing the end of this challenging disease?

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Chronic hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease. It is estimated that between 80 and 160 million people worldwide are infected with this virus.

Chronic renal failure patients infected with HCV represent a very heterogeneous population, with diverse degrees of renal function and, in some cases, already integrated in chronic dialysis programmes (haemodialysis or peritoneal dialysis) or submitted to an organ transplantation (kidney, kidney/liver or kidney/pancreas). Since its discovery in the late 1980s, HCV infection has been posing enormous challenges to nephrologists in each of these groups.

Portuguese nephrologists have been in the frontline in regards to the surveillance, diagnosis and management of HCV-infected hemodialysis patients. The prevalence of anti-HCV serum tests, the use of dedicated dialysis machines, the change in reuse strategies and in some cases separate dialysis rooms have contributed to the well-documented decrease in the prevalence of HCV-positive patients in Portuguese dialysis units, from 9.9% in 1991 to 5.1% in 1993, as was reported in one of the most cited sources on this subject, that by Pinto dos Santos, Alfredo Loureiro and Brian Pereira[1]. Clearly, the screening of all blood-derived products and the development and use of erythropoiesis stimulating agents have also contributed to this change.

In addition to the well-recognised and widely described renal histological lesions associated with HCV infection (namely cryoglobulinaemic-membranoproliferative glomerulonephritis, membranoproliferative glomerulonephritis without cryoglobulin, cryoglobulinaemic vasculitis and membranous nephropathy), HCV chronic infection has also been associated with several pathogenic pathways responsible for the increased morbidity and mortality observed in the uraemic population[2].

In fact, chronic HCV infection in uraemic patients is a systemic inflammation that induces oxidative stress, endothelial dysfunction, and vascular lesions. HCV infection reduces the expression of Insulin Receptor Substract 1 and 2, and increases the renal synthesis of Insulin-like Growth Factor-1 and Transforming Growth Factor-β, as well as the mesangial expression of Angiotensin II receptor. For these reasons, it is not surprising that HCV infection emerges as a strong diabetic risk factor in CKD patients from the early stages of chronic renal failure, during dialysis and after transplantation.

The systemic effects of HCV infection, its inflammation, and diabetogenic and atherosclerotic effects are in accordance with the accelerated decline of renal function, the increased graft lost after transplantation, and the clear and significant increase in mortality observed in dialysis and in transplanted patients infected with HCV, in comparison with those without HCV infection[3].

Until recently, pegylated interferon and ribavirin were the standard therapeutic regimens for those chronically infected with HCV. But these therapies have been associated with many adverse effects, treatment-limiting toxic effects and suboptimum efficacy. With this approach, a sustained virological response (SVR) was usually observed in less than one third of the

patients, even after long treatment intervals of 48 weeks.

In recent years, HCV infection therapy has seen tremendous progress. Several direct acting antivirals (DAAs) have been approved, enabling interferon-free antiviral treatments with high SVR rates. The primary goal of HCV therapy is the eradication of the virus HCV-RNA, which is considered undetectable 12 weeks (SVR 12) or 24 weeks (SVR 24) after end of treatment.

Although there has been a rapid expansion in the number of trials evaluating the use of DAAs in the general population, the most severe chronic kidney disease (CKD) patients have been consistently excluded from these studies.

Until very recently, treatment options for patients with hepatitis C infection and stage 4-5 chronic kidney disease (glomerular filtration rate below 29 mL/min) remained very deficient, as the approved all-oral regimens contain drugs whose metabolites are toxic, cleared almost exclusively by the kidney (as is the case of sofosbuvir). Due to its renal elimination, sofosbovir may only be used in patients with a glomerular filtration rate above 30 mL/min per 1.73 m^2.

Recent reports of second generation DAAs use in patients with CKD stage 4-5 (including dialysis patients) offering a interferon-free, ribavirin-free (in most genotypes), all-oral treatment regimen represent a major change and marked improvement in treatment for this significantly underserved patient group.

The preliminary results from the RUBY-I trial were recently presented and published[4]. In this study, the use of ombitasvir-paritaprevir-ritonavir and dasabuvir (with or without ribavirin) in genotype I infected patients with CKD stage 4-5 was able to assure an SVR of more than 95% after 12 weeks of therapy. This near eradication of the infection after only a short period of treatment is similar to that observed in the non-uraemic population.

This DAAs protocol, of ombitasvir-paritaprevir-ritonavir and dasabuvir (with or without ribavirin), is currently the only one approved in Europe to treat CKD stage 4-5 patients, and also the only one that is presently offered to Portuguese patients.

Another placebo controlled trial, the C-SURFER trial, used Grazoprevir (100 mg) plus Elbasvir (50 mg)/day during 12 weeks and was associated with an SVR 12 of 94% in 122 CKD 4-5 patients with genotype 1 infection[5]. This therapy has already been approved by the FDA and is currently awaiting approval in Europe.

Both therapeutic regimens used in the RUBY-I study and in the C-Surfer study have already been considered and included in HCV infection treatment guidelines from the American Association for the Study of Liver Diseases (AASLD), the Infectious Diseases Society of America (IDSA) and the European Society for the Study of the Liver.

In this issue of the Port J Nephrol and Hypert, Rui Tato Marinho presents an in-depth review of the use of the new DAAs in the treatment of HCV-infected patients. His unique experience, based on participation in several international trials which included patients with severe chronic renal failure, emphasises the relevance of this revision.

Some burning questions and alternative approaches still need to be discussed and, if possible, clarified by the Portuguese nephrology community, such as for instance:

- Which uraemic patients should be screened for HCV infection and how? From CKD stage 1? By the general practitioner/family doctor?
- How frequently should we perform serologic tests for HCV antibodies in our dialysis units?
- How frequently should we perform an HCV-RNA test in this population?
- How should we define “risk population”? (iv drug abuser, hospitalised patient, holidays in HCV “endemic areas”?)
- Who is going to pay for this huge increment in HCV-RNA tests?
- Could Ag-HCV determination be a cheaper and faster way (automatised test) of screening this “high-risk population” in dialysis facilities?
- Effects of HCV therapy on the immune-suppressive drug, after solid organ transplantation.

All these questions and many others were discussed during the first “Consensus Meeting” promoted by the Portuguese Society of Nephrology, the Portuguese Medical Association (College of Nephrology) and our gastroenterology colleagues, which took place in Lisbon on April 1st, 2016.

The HCV antibodies should be used for screening the previously negative patients.

During the remainder of the current year, these topics are subject to open discussion. The next revision of the *Manual de Boas Práticas de Diálise Crónica* will include these proposals and will be published during the first quarter of 2017.

At this moment, and based on the most recent results, it seems clear that the vast majority of patients with CKD stage 4-5 have a unique opportunity to achieve the definitive eradication of HVC. This will dramatically change the prognosis of these patients and the future of HCV-infected CKD patients.

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