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EDITORIAL

HCV-infected dialysis patients: History is changing

Hepatitis C virus (HCV) infection is frequent among patients with an end-stage renal disease (ESRD): they are historically a population at risk of infection (transfusions and transplants from HCV donors and parenteral risk in the dialysis units) on the one hand and HCV infection contributes to occurrence and worsening of the renal function on the other hand [1]. The improvement of serological screening and hygiene together with the introduction of erythropoietin have significantly reduced the risk of HCV infection among dialysis patients [2]. However, the prevalence of the HCV virus is still higher in dialysis patients compared to the general population. According to the Dialysis Outcomes and Practice Patterns Study (DOPPS), HCV prevalence among ESRD patients decreased from 14.7% in 2004 to 8.7% in 2012—2015 while in the general population of the corresponding countries it ranges from 0.4 to 2.0% [3]. As regards to dialysis patients awaiting kidney transplantation, during an observation period between 2012 and 2015, the prevalence of HCV infection ranged from 0% in China and France to 11% in the Gulf Cooperation Council countries [4]. These prevalence data will certainly be modified by the universal access to direct-acting antivirals (DAAs). In fact according to the European association for the study of the liver (EASL) as well as the KDIGO recommendations [5,6], all patient with chronic kidney disease (CKD) should be treated with DAAs, with a prioritization for those patients with ESRD, advanced liver fibrosis or symptomatic cryoglobulinemia. The achievement of a sustained virological response (SVR) is associated with a lowering risk of renal impairment and ESRD-related mortality compared to that of untreated patients [7]: a registry study from Taiwan reported that ESRD-associated mortality was higher among patients with a positive viral load than in non-viremic patients with positive HCV antibodies and in non-HCV-infected patients. Moreover, the negativity of viral load, among patients treated by interferon or DAAs, was associated with a lower risk of ESRD, suggesting an indirect beneficial influence of SVR on renal function [8]. The hazard ratio for adjusted mortality comparing treated versus untreated patients was 0.47, confirming that treatment of HCV should be mandatory for patients undergoing dialysis [9]. The higher mortality of dialysis patients with an active HCV infection is due in part to the higher cardiovascular and diabetes burden and in part to liver complications. HCV plays an atherogenic role by the worsening of each components of metabolic syndrome such as blood hypertension, insulin resistance and diabetes, abdominal obesity and dyslipidemia [10]. Moreover, HCV infection is associated with chronic hepatitis, cirrhosis ad hepatocellular carcinoma. In a recent prospective study, data from 76,689 patients (DOPPS population) were collected between 1996 and 2015. Casemix adjusted hazard ratios (95% confidence intervals) for HCV positive versus HCV negative patients were 1.12 (1.05 to 1.20) for all-cause mortality, 5.90 (3.67 to 9.50) for hepatic-related mortality, 1.09 (1.04 to 1.13) for all-cause hospitalization, and 4.40 (3.14 to 6.15) for hepatic-related hospitalization [11]. Besides, in a meta-analysis including a total of 145,608 dialysis patients, the HCV antibodies positivity was an independent and significant risk factor for mortality. In fact, the adjusted relative risk (95% confidence interval) was of 1.35 (1.25—1.47). Interestingly, not only liver-related deaths [adjusted relative risk 3.82 (1.92; 7.61)] but also cardiovascular mortality [adjusted relative risk 1.26 (1.10; 1.45)] constituted the causes for the increased mortality observed in HCV positive ESRD patients compared with HCV negative patients [12]. HCV infection is not only associated with a higher mortality during dialysis but also after renal transplantation. In fact, graft survival is lower among patients with HCV infection, as compared to uninfected patients. Indeed, HCV infection in renal transplant recipient is an independent risk factor for graft loss since it favorize chronic rejection, transplant glomerulopathy, proteinuria, post-transplant diabetes, and HCV-associated glomerulonephritis [13]. Renal transplant recipients with chronic hepatitis C have also a reduced survival compared with that of transplant recipients without HCV infection, as a consequence of liver disease, cirrhosis-associated sepsis,

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and increased incidence of adverse events of the immunosuppressive therapy [13]. The timing of antiviral therapy before or after kidney transplantation in patients with ESRD is still an issue. Before the introduction of DAAs, the treatment of HCV in dialysis patients was done before renal transplantation due to the risk of graft dysfunction or rejection with interferon-based therapy. Currently, international guidelines recommend prescribing DAAs to all patients whatever the stage of liver fibrosis and whether or not they are candidates for kidney transplantation, since HCV infection is associated with higher extra-hepatic mortality and morbidity, especially renal deterioration and diabetes in ESRD patients [10]. From a practical point of view, the choice of treating patients on dialysis is based on the severity of liver disease and on the timing of kidney transplantation depending also on the type of donor (deceased versus living donors). Procrastinating antiviral treatment after renal transplantation may be a possibility as it allows the patient to receive a HCV positive organ reducing his waiting list time. However, some clinicians, considering the short duration of current antiviral treatments (8 to 12 weeks), prefer to treat patients as soon as possible, also regarding the prognostic worsening of HCV positive patients on dialysis and to avoid potential drug—drug interactions with calcineurin inhibitors used as immunosuppressive therapy after renal transplantation. Concerning renal transplant, according to the Organ Procurement and Transplantation Network (OPTN), over 100,000 patients are waiting for a kidney transplant with an annual increase of 2%—10%. This organ scarcity leads to waiting times that exceed 3 to 5 years in the United States. Due to rate of mortality on dialysis and the long wait times on list, it is estimated that more than 25% of patients on the waitlist will die prior to obtaining an organ [14]. In 2013, in France, 4467 new patients were waitlisted for kidney transplant, 14,336 patients were on the waiting list and only 3074 transplants were performed. In France the median waiting list time raised from 1.2 to 2.3 years between the 1999 and 2013 [15]. Despite this shortage of organs more than 800 kidneys from deceased donors with HCV infection were declined in the United States in 2016. The cause of this refusal was mainly due to the low efficacy of the antiviral treatments available before the DAAs, with an accelerated risk of cirrhosis and liver failure for the recipient, and to the potential rejection of the organ in cases of interferon-based therapy. A limited but growing number of evidences suggest that DAAs treatment can provide high cure rates for immunosuppressed patients with HCV. The pilot study Transplanting Hepatitis C Kidneys into Negative Kidney Recipients (THINKER) reported HCV cure among all 20 HCV negative patients transplanted with HCV-infected kidneys [16], indicating a median term good outcome also for those patients transplanted with an infected kidney, thanks to these novels antiviral therapies. Early trials are promising, but larger trials and a plan for obtaining HCV therapy in the post-transplantation period are needed. In a recent English study between 2009 and 2016, 120 patients identified from the Potential Donor Audit were reject because of the presence of HCV infection. Between 2000 and 2015, 244 HCV positive deceased donors were identified from the UK Transplant Registry, and 76 (31%) proceeded to donation (63 liver, 27 kidney, and 2 heart transplants). Recipient and graft survival was not negatively affected by donor HCV status. A cost analysis was also performed and the additional costs of treating recipients receiving HCV positive kidney was cost-neutral with dialysis 5 years from transplantation [17].

One other possibility would be to treat potential living donors before donation. This would allow a greater availability of organs from non-viremic patients. In our center, we reported a case of a positive HCV donor who donated a kidney to his daughter after obtaining an SVR with DAAs. Currently 2 years after renal transplantation, both the donor and the recipient are HCV RNA negative, demonstrating the complete virologic recovery after DAAs treatment [18].

Probably in the near future a combination of the availability of DAAs, the expanding use of hepatitis C-viremic kidney donors, the preventive cure of potential living donors together with the awareness of the donation of organs will improve the prognosis of HCV-infected dialysis patients awaiting renal transplantation trough the virologic cure and the reduction of waiting list time.

Disclosure of interest

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Lucia Parlati[a,*]
Stanislas Pol[b]
[a] *Université Paris Descartes, Hepatology Department, Cochin Hospital, AP—HP, UPMC, 75014 Paris, France*
[b] *Université Paris Descartes, Hepatology Department, Cochin Hospital, AP—HP, Inserm U1223, UMS-20, Center for Translational Science, Institut Pasteur, 75014 Paris, France*

* Corresponding author.
E-mail addresses: lucia.parlati@aphp.fr (L. Parlati), stanislas.pol@aphp.fr (S. Pol)
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