

Treatment of HCV in Dialysis Patients

Stansilas Pol, MD, PhD



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Hepatitis C virus (HCV) infections are frequent in hemodialysed patients and are mainly related to blood transfusions but also to the nosocomial transmission in hemodialysis centers or by the transplantation of an infected graft. HCV infections appear to be associated with a significant impact in terms of morbidity or mortality of dialysis patients and of kidney recipients. This impact justifies liver pathological evaluation in dialysed patients, in order to discuss potential antiviral treatments which will take into account the age, co-morbidities, the severity of the liver disease and a potential candidacy for renal transplantation.

1. Why to treat?

The frequency, the risk of community-acquired transmission and the clinical impact of HCV infection on morbidity and mortality are the reasons to evaluate and treat HCV infection in dialysis patients.

HCV infection is frequent in patients with end-stage renal failure treated by chronic hemodialysis with a prevalence varying from 10 to 65% according to the geographical area related to both transfusions before 1990 and nosocomial contamination. Higher is the prevalence in dialysis patients, higher is the risk of nosocomial contamination.

Little is known about the clinical impact of HCV infection on morbidity and mortality in hemodialysis patients but most studies have suggested a decreased survival in HCV-infected dialysis patients (from 52 to 32% at 8 years). It is related to liver disease with necroinflammatory activity and fibrosis which are present in 79% of HCV-infected dialysis patients, including 11% of cirrhosis. In kidney recipients, most of recent studies but not all with a long-term follow-up, indicate decreased both allograft and patient survivals in HCV-positive as compared to HCV-negative kidney recipients more than 5 years after transplantation. Finally, it has been suggested that HCV-infected hemodialysis patients survival was better after renal transplantation than after dialysis continuation.

These general characteristics underline the need of antiviral treatments in hemodialysed patients with active or fibrotic liver disease, in those who are candidates to kidney transplantation and in kidney allograft recipients with severe liver disease.

2. How to treat?

Preventive treatment is efficient but should not be discussed.

In the general population, standard therapy is the combination of α -interferon and ribavirin with a rate of sustained virological response around 40% with standard interferon and 50% with pegylated interferon.

Ribavirin is contraindicated in patients with renal failure (as defined by a creatinemia over 200 $\mu\text{mol}/\text{l}$); indeed, for pharmacokinetics reasons (accumulation of ribavirin metabolites in erythrocytes) there is a risk of enhancement of the ribavirin-related hemolytic anemia with deep and long-lasting fall of the hemoglobin levels, despite an increase in erythropoietin doses.

Thus, interferon is used in monotherapy with standard schedule: 3 MU subcutaneously three times weekly and after each hemodialysis during 6 to 12 months.

In dialysis patients, the biochemical and virological efficacy of interferon monotherapy is, at least, as good as in the general population with 20% to 90% rate of viral eradication according to the dose and the duration of the treatment. Moreover, a histological improvement is common, even in the absence of virological efficacy. Tolerance is poorer than in non hemodialysed patients since treatment discontinuation is necessary in 20 to 40% of cases with a high incidence of cardiovascular side-effects, anemia, erythropoietin resistance and general symptoms (weight loss). Persistence of detectable viremia 2 months after the beginning of treatment may predict the absence of sustained response and may result in treatment discontinuation if the therapeutic purpose is only virological (viral eradication), in a candidate to renal transplantation for

example; treatment could be continued if the therapeutic aim is also an histopathological improvement in an hemodialysed patient with severe liver disease.

The higher efficacy, as well as, the poorer tolerance could reflect the significant higher pharmacokinetics area under curve of α -interferon reflecting an increase of the half-life (10 vs. 6 hours) and of the concentration of interferon by a decrease in renal clearance in dialysis patients (43). This raises the question of the use of the long lasting (pegylated) interferon in dialysis patients, even if pharmacokinetics curves suggest that dialysis is not a contraindication. In the future there is a need to evaluate:

1. The long term clinical benefit provided by the antiviral therapy (as in the general population), especially in those patients who underwent a renal transplantation;
2. The risk of viral recurrence after renal transplantation. In a recent study, 29 hemodialysed patients were treated during one year and 64% had sustained viral clearance; 14 were transplanted: 8 patients among the 9 responders had undetectable viremia after a mean follow-up of 41 months.

3. When to treat pragmatically?

Pragmatically, like in the general population, a liver biopsy should be performed in case of viral hepatotropic infection in hemodialysis patient without overt co-morbidities by transvenous way. The liver biopsy allows to assess the grade and the stage of the liver disease (necro-inflammatory activity and fibrosis).

In dialysis patients who are not candidates to renal transplantation, antiviral therapy is recommended in patients with fibrotic disease and the aim of therapy is viral eradication but also potential reduction of fibrosis. In dialysis patients who do not receive antiviral treatment, serial (each 5 years?) liver biopsies should be considered in order to early detect pathological deterioration and to treat.

In candidates to renal transplantation, cirrhosis (and extensive fibrosis) are contra-indications to renal transplantation: a combined liver-kidney transplantation may be proposed. In candidates to renal transplantation, treatment has to be proposed because α -interferon therapy is inefficient and deleterious after transplantation. Even in patients with mild liver disease, antiviral treatment may be proposed in order to obtain viral eradication before transplantation which allows to avoid liver deterioration and risks of HCV-related de novo glomerulonephritis; in this situation, treatment may be discontinued after 2 months of therapy if HCV RNA remains detectable since there is no chance of delayed viral eradication.

Finally, in case of acute hepatitis C, a situation observed in the dialysis setting with an annual incidence of 2.6%, interferon is also efficient: a viral clearance was obtained in 26% and 51 % of hemodialyzed patients treated by 3 MU and 6-10 MU for 3 months (by comparison with spontaneous clearance of 5.6%), respectively. A recent study of the treatment of acute hepatitis C in the general population reports a 98% rate of sustained virological response to interferon alone (5 MU daily for 4 weeks and 3 times weekly for 20 weeks): this optimized schedule may be proposed in hemodialysis patients but there is a risk of poor tolerance.

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