Hepatitis C in Dialysed Patients – What Is the Current Optimal Treatment?

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Key Words

Hepatitis C · End-stage renal disease · Dialysis ·
Interferon alfa · Peginterferon · Ribavirin

Abstract

Hepatitis C virus (HCV) infection is an important cause of morbidity and mortality in the dialysis population. The problem is more pronounced after renal transplantation. It seems that immunosuppressive drugs facilitate HCV replication and accelerate hepatic lesions. Interferon is not recommended after renal transplantation because of the risk of acute rejection and graft dysfunction, and for this reason it is important to eradicate HCV RNA before transplantation. Prevention is the most important treatment measure. Good clinical practice together with screening of blood products and organs is of outstanding importance. Pegylated interferon (PEG-INF) and ribavirin are currently considered to be optimal therapy for HCV infection. Pegylation delays clearance of interferon, which leads to a more potent and longer antiviral effect. The two PEG-INF formulations (alfa-2a and alfa-2b) with different pharmacokinetic characteristics are currently available. Their clearance is reduced by almost 45% in patients with end-stage renal disease. Taken together with the high prevalence of adverse effects associated with

the PEG-INF, an increased awareness of their use in dialysis patients is reasonable. There are few published studies on interferon and PEG-INF therapy in uremic patients. These studies confirm that the rate of response to different interferon formulations in dialysis is much higher than in the general population, but with a higher rate of adverse events. Ribavirin increases the response rate to treatment with PEG-INF. Great caution is warranted on its use in dialysis patients, whereas in patients with renal disease it accumulates and causes a dose-related haemolysis. Current results are encouraging but limited by a small number of patients and short follow-up. Multi-centre, controlled studies with longer follow-up are needed to establish an optimal protocol for the treatment of chronic HCV infection in dialysis patients.

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Hepatitis C virus (HCV) infection is a common problem in dialysis patients with the prevalence ranging from 1 to 63% [1]. HCV transmission occurs mainly through exposure to infected blood. Infection may spread through contaminated haemodialysis equipment or unsafe medical practices. Patient-to-patient transmission of HCV with transplanted organ has been reported. Although previous reports have suggested a benign clinical and histological course of HCV infection in dialysis patients, current investigations demonstrate all grades of chronic hepatitis including liver cirrhosis [2]. HCV infection has been identified as an important cause of morbidity and

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mortality in dialysis patients [3]. Hepatitis C-positive recipients have an increased risk of chronic liver disease and mortality after renal transplantation compared with HCV-negative patients [4]. According to the results of Pedroso et al. [5], HCV infection adversely affects patient and graft survival and increases the risk of death from infections. Interferon is not recommended after renal transplantation because of the risk of acute rejection and graft dysfunction, and for this reason it is important to eradicate HCV RNA before transplantation [6].

This article summarizes the current understanding of HCV infection in dialysis patients with emphasis on its treatment.

Epidemiology of Hepatitis C in Dialysis Patients

Long-term kidney disease, multiple blood transfusions and/or organ transplant before 1992 and potential exposure to nosocomial infections in dialysis units make dialysis patients especially vulnerable to the development of hepatitis C and other blood-borne infections. There is substantial variability in the prevalence of chronic HCV infection among dialysis patients worldwide. Lower socioeconomic status of the country has been associated with an increased prevalence of HCV infection, mainly due to insufficient resources for treatment with erythropoietin and for maintenance of dialysis units. In the era of screening tests that exclude infected blood or donors, HCV is rarely transmitted by blood transfusion or transplantation. However, despite all these advances, HCV infection remains a significant problem even in industrialized countries [1]. Dialysis units with an increased prevalence of HCV also have an increased incidence of the infection. Strategies to control nosocomial transmission of HCV should be implemented in all dialysis units. Besides standard universal precautions like the use of gloves and restricted use of common supplies, special attention should be focused on careful disposal of dialysers and blood tubing after haemodialysis sessions. Strict isolation of HCV-positive patients is usually not recommended. However, it might be a useful measure for prevention of nosocomial spread of HCV in dialysis units with a high HCV prevalence [7]. Available data demonstrate that patients with HCV infection may be included in dialyser reuse programs. Patients should be regularly monitored. In Croatia, all dialysis units test their patients and staff for anti-HCV. Surprisingly, only 62% of the centres in the USA have introduced routine testing for HCV in dialysis patients [1]. In the 9-year study of 6,412 patients starting

dialysis in Italy, Di Napoli et al. [8] found a decrease in anti-HCV prevalence from 30.6 to 15.1% that could be related to the higher mortality of HCV-positive patients compared with HCV-negative subjects.

Natural History of HCV Infection in Dialysis Patients

The natural history of HCV in dialysis patients is not completely understood. The reduced long-term survival combined with slow progression of the HCV-associated liver disease may mask the consequences of HCV infection in the dialysis population. Reports on the natural history of hepatitis C infection in the dialysis population vary. Previous studies that focused on liver disease demonstrated a low proportion of HCV-positive dialysis patients with bridging hepatic fibrosis or cirrhosis. In a multi-centre prospective study, Nakayama et al. [9] demonstrated an increased risk of death in HCV-positive patients due to cirrhosis and hepatocellular carcinoma. Okuda and Yokosuka [10] compared 189 HCV-positive dialysis patients with 378 sex-/age-matched controls without uraemic syndrome. Of 25 dialysis patients who were followed up for more than 15 years, 15 patients were HCV RNA negative. None of them progressed to cirrhosis. During the same period none of the controls had lost HCV RNA, and one quarter to one third of them progressed to cirrhosis. The possible explanation for such a distinct difference is reduction of the viral load via adsorption of viral particles onto the dialyser membrane with their subsequent destruction [10]. Badalamenti et al. [11] observed an increased level of circulating interferon- α after HD sessions. They suggest lymphomonocyte activation as an additional mechanism for the mild course of hepatitis C in dialysis patients.

Diagnostic Approach

Various tests are available for the diagnosis and follow-up of HCV infection. Serological tests of the third generation are highly sensitive and specific, and are suitable for screening of dialysis patients. False-negative tests are nowadays rare, while false-positive tests may occur in dialysis patients with autoimmune disorders or other infections. Confirmation of HCV infection is obtained by qualitative or quantitative HCV RNA assay. ALT is a helpful although non-specific marker of the presence of HCV infection in the dialysis population. Serial determinations of ALT imprecisely reflect the severity of liver

disease and do not correlate with the liver histology or viral load. Only liver biopsy provides information on the extent of HCV-associated liver disease. This invasive procedure is associated with an increased risk of bleeding in dialysis patients. Transjugular biopsy is associated with a lower risk, and nowadays liver biopsy seems mandatory to evaluate the severity of liver disease in order to choose the most suitable treatment option [6, 12].

According to our experience, all patients with end-stage renal disease (ESRD) should be screened for HCV with serological test before starting renal replacement therapy. In case of positive serology, viral load should be determined by HCV RNA. In addition, qualitative HCV RNA should be determined at least once in each patient to discover patients that have 'escaped' lower-sensitivity tests.

Treatment of HCV Infection in Dialysis Patients

The most important treatment option is prevention of infection. Elimination of the virus from the infected host is a difficult task. According to the current knowledge, interferon therapy is considered as the main treatment option in all patients with HCV-infection associated liver disease. Despite the fact that HCV infection adversely affects the survival of dialysis and renal transplant patients and its high prevalence in these groups of patients, large clinical trials are lacking.

Interferon Alfa

Interferon alfa is a non-glycosylated serum protein that is induced by exposure to foreign antigens. After filtration at the glomerulus, interferon alfa is reabsorbed in proximal tubules where it undergoes proteolytic degradation. Elimination half-life of interferon alfa is increased in patients with renal failure. Several interferon-alfa formulations have been developed for therapeutic use in humans (alfa-2a, alfa-2b, alfa-n1).

The optimal treatment protocol for interferon monotherapy in HCV-positive dialysis patients remains unclear. Fabrizi et al. [13] evaluated 14 clinical trials and demonstrated that more than 37% of HCV-positive dialysis patients may be successfully treated by interferon monotherapy. Sustained virological response (SVR) defined as undetectable HCV RNA at 6 months after treatment was achieved by only 7–16% of patients with chronic HCV infection and normal renal function [14]. Better therapeutic response may be explained by lower viral load in uraemic patients, alterations in the pharmacoki-

netics of interferon in renal failure, and possibly by improvement of the immune response in dialysis patients induced by interferon.

Adverse events were not only more common but also more severe in dialysis patients. Besides pancytopenia, flu-like syndrome, neurological disorders and gastrointestinal problems, severe side effects included cerebral haemorrhage, pulmonary oedema, acute pancreatitis and cardiomyopathy [13]. The drop-out rate was 17% [13], compared to 5–9% in patients with normal renal function [14]. Drug accumulation, comorbidities and advanced age may enhance toxicity and explain the lower tolerance of interferon in dialysis patients.

Grgurević et al. [15] evaluated two different therapeutic protocols for dialysis patients: 8 patients were treated with INF-alfa 3×3 MU/week s.c. for 6 months (group A), and 7 patients were treated with INF-alfa 3×5 MU/week for 3 months, then 1×5 MU/week for another 3 months (group B). The end of treatment response was 87.5% in group A and 28.5% in group B, the difference being statistically significant ($p < 0.05$). Although better SVR (50 vs. 28.5%) and lower drop-out rate (0 vs. 28.5%) were achieved in group A compared to group B, these differences did not reach statistical significance [16]. Therapy with INF-alfa 3×3 MU/week s.c. for 6 months seems to be more appropriate for the treatment of HCV in dialysis patients, mostly due to better tolerability, i.e. lower drop-out rate. These differences could be attributed to different pharmacokinetic properties of the particular therapy protocol. Urbanek et al. [17] demonstrated that early diagnosed HCV infection in dialysis patients could be more efficiently treated than chronic infection. Patients were treated with INF-alfa 2B 10 MU administered daily for 21 days followed by 3 MU administered 3 times weekly for 12 weeks. They obtained a SVR in 72% of patients without any serious side effects of treatment.

Pegylated Interferon

Modification with polyethylene glycol (PEG) reduces clearance of interferon. Two formulations of PEG-interferon (PEG-INF) have been developed: (1) pegylated interferon alfa-2a (PEG-INF alfa-2a), obtained by conjugation of a 40-kDa branched PEG polymer to lysine residues to interferon alfa-2, and (2) pegylated interferon alfa-2b (PEG-INF alfa-2b) with a single 12-kDa linear moiety attached to interferon alfa-2b [17]. While PEG-INF alfa-2b is cleared by the kidneys, PEG-INF alfa-2a is metabolized in the liver. The PEG moiety is inert and is removed from the body in 50–60 days. Different pharmacokinetic parameters (table 1) result in different timing of the occur-

rence of adverse effects. Alfa-2b peginterferon is associated with a rapid onset of side effects. Side effects of alfa-2a peginterferon gradually increase during the first several weeks of treatment [18].

Pharmacokinetic studies in dialysis patients have shown marked elevation of blood levels of PEG-INF alfa-2b, but not of PEG-INF alfa-2a. Clearance fraction of PEG-INF alfa-2a decreased from 94 ml/h in controls to 63 ml/h in ESRD patients, increasing its half-life from 52 to 58 h [19]. A dose of 135 µg PEG-INF alfa-2a in ESRD patients resulted in similar serum levels as a dose of 180 µg in patients without renal failure. A weekly dose of 0.5–1.0 µg/kg of PEG-INF alfa-2b has been suggested for patients with ESRD [6].

Clearance of PEG-INF alfa-2a and PEG-INF alfa-2b may differ depending on the pore size of dialysers. A 40-kDa PEG-INF alfa-2a was not cleared through dialysers with pore sizes <100 Å. In contrast, PEG-INF alfa-2b was cleared through dialysers with pore sizes >60 Å. These results suggest the possibility to improve the efficacy of PEG-INF treatment with the use of appropriate dialysers. This issue needs confirmation by in vivo studies [20].

Pegylated interferons have been more efficient in treatment of chronic HCV infection than standard interferons [21]. However, data on the efficacy and safety of peginterferons in the dialysis population are limited (table 2).

Sporea et al. [22] used 180 µg of PEG-INF alfa-2a for 48 weeks in 10 HCV-positive dialysis patients. The drop-out rate was 40%. Two patients stopped treatment because of non-compliance, 1 patient died from cerebral haemorrhage, and 1 patient developed sepsis secondary to central venous catheter insertion. Three of 6 (50%) patients that completed the 48-week treatment had a SVR. However, the intention-to-treat analysis showed SVR in only 30% (3 of 10) of patients. All patients experienced side effects related to the use of PEG-INF, without the

need to discontinue the treatment [22]. Annicchiarico and Siciliano [23] report the results of their study in which 6 patients received PEG-INF alfa-2b for 24 weeks. SVR was 33%. Teta et al. [24] treated 3 patients with PEG-INF alfa-2a. The starting dose of 180 µg/week was reduced in 2 patients because of cytopenia and other side effects (insomnia, depression, weight loss, flu-like symptoms and cutaneous bullous lesions). They completed their treatment with a weekly dose of 90 µg. Recently, Kokoglu et al. [25] prospectively followed up 12 patients who received 135 µg of PEG-INF alfa-2a weekly for 48 weeks. All patients were interferon naive. Another 13 dialysis patients with HCV infection served as controls. End-of-treatment virological responses were 83.4% in the treatment group and 7.7% in the control group. SVR was achieved by 75 and 7.7% of patients, respectively. These results are encouraging. Although all patients experienced adverse effects related to PEG-INF, they completed their 48-week treatment. The most common side effects included anaemia, fatigue, thrombocytopenia and leucopenia [25]. Covic et al. [26] published in 2006 results of treatment of 78 dialysis patients with PEG-INF alfa-2a. An early viral response was obtained in 61.5% of patients. However, a high rate of non-compliance and adverse

Table 1. Pharmacokinetic parameters of two PEG-INF alfa formulations

Parameter	PEG-INF alfa-2a	PEG-INF alfa-2b
Clearance, ml/min	725	60
Absorption half-life, h	4.6	5.0
Elimination half-life, h	20	80
Time to peak serum concentration, h	20	80

Table 2. Trials with pegylated interferon alfa-2a in dialysis patients with chronic HCV infection

Group (first author)	Patients	PEG-INF type	Dose µg/week	Duration weeks	ETR rate	SVR rate, %	Drop-out rate, %
Sporea, 2006 [22]	10	Alfa-2a	180	48	87.5	30	40
Teta, 2005 [24]	3	Alfa-2a	180	24–48	67	67	0
Kokoglu, 2006 [25]	12	Alfa-2a	135	48	83.4	75	0
Covic, 2006 [26]	78	Alfa-2a	135	48	19.2	14.1	73.1

PEG-INF = Pegylated interferon; ETR rate = end-of-treatment response rate (absence of HCV RNA at the end of treatment); SVR rate = sustained virological response (absence of HCV RNA 6 months after stopping therapy).

events caused discontinuation of therapy in 73.1% of patients. Thus, only 21 patients reached week 48 on therapy, and only 19.2% of the initial intention-to-treat population had undetectable HCV RNA levels. Sustained viral response was recorded in only 11 patients (14.1%). These results are not encouraging, and they do not support the superiority of PEG-INF alfa-2a monotherapy. A large multi-centre study of PEG-INF treatment in dialysis patients has started in the USA [6].

Interferon and Ribavirin

The combination of PEG-INF and ribavirin is now the standard treatment for patients with chronic hepatitis C and normal renal function. Ribavirin is cleared predominantly in the kidneys and causes a dose-related haemolysis. Haemodialysis does not change its serum concentration, thus ribavirin is considered to be contraindicated in patients with renal failure who are especially vulnerable to its toxic effects due to pre-existing anaemia and low-grade haemolysis associated with renal failure and dialysis [6].

Several small studies of ribavirin therapy in patients with renal failure have been published. A preliminary report by Tan et al. [27] who treated 5 patients with interferon alfa-2b and ribavirin describes the high incidence of side effects with a drop-out rate of 40%. Four patients developed virological response during the treatment. Bruchfeld et al. [28] treated 6 ESRD patients with interferon alfa-2b and ribavirin. Ribavirin was regularly monitored and the dose adjusted to achieve serum concentrations of 10–15 µmol/l. Five patients achieved an end-of-treatment virological response. SVR occurred in only 1 patient. Adverse effects were common despite the use of erythropoietin. The same group investigated the efficacy and safety of pegylated interferon in combination with ribavirin in dialysis patients [29]. Six haemodialysis pa-

tients were treated with PEG-INF alfa-2a 135 µg/week (n = 2) or PEG-INF alfa-2b (50 µg/week) (n = 4) for 24 (genotype 2) to 48 (genotypes 1 and 4) weeks with the ribavirin dose modified according to plasma concentration. Anaemia was treated with iron and high doses of erythropoietin. All patients achieved virological and biochemical response. SVR was achieved in 3 (50%) patients. Adverse events were quite frequent. One young patient died from heart failure associated with severe coronary atherosclerosis. Anaemia was treated with iron and high doses of erythropoietin. No blood transfusions were necessary [29].

These results indicate that ribavirin can be used for treatment of chronic HCV infection in dialysis patients but with extreme caution and only in strictly controlled clinical trials. Erythropoiesis should be appropriately supported. Preliminary reports indicate that it may be necessary to evaluate cardiovascular status before treatment [29]. It is probable that patient who died while treated with PEG-INF and ribavirin [29] had pre-existing significant coronary atherosclerosis, which is no surprise despite his age, as he had been on dialysis for 12 years.

Conclusion

Pegylated interferons are the mainstay of therapy for chronic hepatitis C. Currently available data on using PEG-INF in patients with ESRD are contradictory. However, treatment results seem better than those achieved by patients with chronic HCV infection and normal renal function. Use of ribavirin should still be limited to clinical studies. Results obtained in recent clinical trials should be confirmed by large prospective, multi-centre studies.

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