Combination of interferon alpha and ribavirin in the treatment of hepatitis C: implications for the clinical nephrologist

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Introduction

Hepatitis C virus (HCV) infection is very frequent among patients with end-stage renal disease (ESRD). Recent studies have shown that HCV may increase the risk for death in the haemodialysis (HD) population and appears to have a deleterious impact on long-term graft and patient survival among renal transplant recipients [1]. Furthermore, HCV results in a significantly increased risk of kidney allograft failure and death among kidney-pancreas transplant patients.

While important advances have been made in pre-
venturing hepatitis C, therapy for this disease among ESRD patients remains unsatisfactory. In fact, valid animal models and effective cell culture systems with which to study HCV are lacking.

At present, the most important therapy for hepatitis C in ESRD patients is interferon (IFN), but it is expensive and has limited efficacy and safety. Alternative approaches based on new formulations of IFN are currently under way and combinations of IFN with nucleotide analogues (i.e. ribavirin) are giving encouraging results in the treatment of chronic hepatitis C among patients with normal renal function [2–4]. These findings may have a clinical impact on the therapy for hepatitis C among ESRD patients.

In this report, we briefly summarize the therapeutic options for the treatment of hepatitis C in ESRD highlighting the most recent and novel advances in this field.

Interferon treatment of HCV in ESRD

The only therapeutic regimen that has been proven to be effective in chronic HCV infection among ESRD patients is IFN (mostly IFN-α). IFN-α exhibits a variety of antiviral, immunomodulatory and antiproliferative activities. The mechanisms through which IFNs operate are only partially understood.

Numerous reports [5] have been published regarding the IFN treatment of hepatitis C among dialysis patients. They mostly concern uncontrolled trials showing a rate of immediate and sustained biochemical, histological and virological response similar to patients with normal renal function.

The only double-blind, controlled trial on IFN therapy of HCV in HD patients is that of Fernandez et al. [6], who observed a short-term biochemical response that was significantly higher in the IFN group than among placebo patients. The biochemical and virological response 12 months after therapy was also higher in the IFN group compared with controls; however, this difference was not statistically significant.

However, the vast majority of trials concerning IFN in dialysis are biased by the fact that only patients with biochemical and/or histological evidence of chronic active hepatitis have been selected. These patients show more severe disease and are less likely to have a sustained response.

The mechanisms responsible for the relatively high sustained response to IFN in dialysis patients in spite of the immune compromise conferred from chronic uraemia are unclear. HD patients with HCV have a low viral load. IFN could help to restore the cell-mediated immunity depressed by chronic uraemia, an increase of IFN activity during HD sessions has been shown recently [7]. In addition, it has recently been discovered that the clearance of IFN-α is about half that in a dialysis population compared with non-ureaemic patients [8]. The response to IFN is also associated with numerous host- and virus-related factors. HCV genotype 1b and mild liver pathology are favourable factors for a sustained response among an ESRD population with HCV. Duration of disease, source of HCV infection, iron status, patient age and HCV quasispecies diversity all play a role in the IFN response among patients with normal renal function, but their influence among ESRD patients with HCV is unclear.

A high side-effects rate of IFN therapy in HD has been observed in some studies. The most important side-effects are flu-like symptoms (which respond well to the administration of paracetamol), weight loss, hypoalbuminaemia, anaemia with resistance to erythropoietin, and depression of leukocytes and thrombocytes. It is possible that the altered pharmacokinetic parameters of IFN in chronic uraemia may, to some extent, explain the numerous side-effects found by some authors.

IFN has been used to facilitate renal transplantation in patients on dialysis with chronic HCV who are renal transplant candidates. In some individuals a persistent biochemical response after renal transplantation has been observed; in one patient histological progression did not occur. However, no virological data were available at follow-up [9].

IFN has also been used in the treatment of HCV after renal transplantation; however, it failed to clear HCV RNA and the tolerance of the drug was poor. A high incidence of renal dysfunction, including renal failure and acute allograft rejection has been observed in association with IFN use in transplant recipients. At present, it cannot be recommended for general use in kidney transplant recipients.

Novel treatments for HCV in ESRD

Alternative approaches based on higher doses of IFN-α (up to 30 million per week) or a longer duration of treatment (18–24 months) remain to be explored in ESRD. However, these schedules are likely to be costly.

The efficacy of various types of interferon (i.e. IFN-β, IFN-con-1) is still uncertain in ESRD. It is possible that some of them will show high efficacy. IFN-alphacon-1, also called consensus IFN, is the first bioengineered IFN. In fact, it is a wholly synthetic type I IFN developed using various portions of other IFNs resulting in a consensus sequence. More recently, long-acting α-IFNs have been developed by covalent modifications of the IFN molecule using polyethylene glycol (pegylation). The ‘pegylated’ IFNs can be administered weekly and provide more sustained levels of α-IFN.

It is worthwhile recognizing that although IFN treatment may be associated with favourable effects on biochemical and virological markers, its effects on quality of life and disease progression remain undetermined.

New classes of drugs, such as HCV NS3 protease and helicase inhibitors promise to be highly effective in lowering or suppressing viral replication. They are based on extensive research about the molecular struc-
ture of HCV, which indicates several potential means of inhibiting viral replication.

**Combination of IFN-α and ribavirin**

Most recently, combinations of IFN-α plus ribavirin, an oral nucleoside analogue, have been evaluated. Ribavirin is a synthetic guanosine analogue with activity against a broad spectrum of DNA and RNA viruses, and which shows direct antiviral and immunomodulatory effects. It is approved for use in the USA in aerosol form as therapy for respiratory syncytial virus infection in infants. Treatment with ribavirin alone has no effect on serum HCV RNA levels, although it does lead to a transient decrease in aminotransferase levels. Large multicentre, randomized and controlled trials have recently been developed expanding the preliminary experience on the higher efficacy of the combination of IFN plus ribavirin compared with IFN alone. These trials have indicated that the simultaneous administration of ribavirin and IFN represents an important advance in the treatment of hepatitis C among patients with normal renal function [2–4]. The standard schedule currently proposed is the concomitant administration of 1,000/1,200 mg of ribavirin orally each day plus 3,000,000 IU (3 MU) of IFN thrice weekly for 6 months. The rate of sustained response was 31–38% when combination therapy was used in IFN-naive patients and 49% when used to treat relapers. These rates are several times higher than those obtained with IFN alone.

The simultaneous administration of IFN and ribavirin has also been reported to be more effective than IFN alone in patients unresponsive to a previous IFN therapy. In contrast, the sequential administration of ribavirin alone followed by IFN monotherapy was not effective in patients who did not respond to IFN.

The mechanisms of the antiviral action of ribavirin appear to be related to the inhibition of the viral RNA-dependent RNA polymerase by depleting intracellular guanine pools and interfering with the ‘capping’ of viral RNA. The hypothesis of an immunomodulatory activity of ribavirin needs further evidence [10].

The enhanced effect of IFN-α and ribavirin in combination could be explained by a synergistic antiviral effect on HCV, as shown in vitro with other RNA viruses. However, the exact mechanism of this synergistic antiviral effect is unknown at present. The most frequent side-effect of ribavirin is a dose-dependent red cell haemolysis, which in rare cases can be severe enough to require the discontinuation of treatment. In addition, ribavirin is teratogenic and must be used with caution in women of childbearing age. What is needed most to advance the field of therapeutics in hepatitis C among ESRD patients is the development of large prospective, controlled and randomized trials to evaluate the efficacy, tolerance and safety of this combination regimen. In fact, ESRD patients warrant separate evaluation in view of their immunosuppressed state and the risk of hepatic flare after renal transplantation. Effective therapy for hepatitis C in ESRD is an important goal made more important by the poor prospects for an effective vaccine against HCV.

**Conclusions**

An effective and safe therapy for hepatitis C in ESRD is not yet available. Trials with new IFN formulations are under way, and some of them promise to be highly effective. The role of these newer formulations in the ESRD population remains to be established. Synergistic combination regimens (i.e. IFN plus ribavirin) aimed at maximizing the antiviral activity promise to be an important advance in the therapy of HCV in ESRD. Large prospective, controlled and randomized trials are clearly warranted in order to verify the efficacy, tolerance and safety of concomitant administration of IFN and ribavirin for HCV in ESRD. In the meantime, it is appropriate to evaluate IFN therapy for patients on dialysis who have HCV and who are serious renal transplant candidates.

**References**