Relevance of low viral load in haemodialysed patients with chronic hepatitis C virus infection

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AIM: To identify predictors of sustained virological response in hemodialysed patients treated by Peginterferon α for chronic hepatitis C, genotype 1.

METHODS: The sustained virological response (SVR) rate, IL28B genotype, IFNL4 genotype, initial viral load (IVL) and other pretreatment variables in 39 end-stage renal disease patients (ESRD) on maintenance haemodialysis (HD) infected with hepatitis C virus (HCV), genotype 1b, were compared with a control group of 109 patients with normal kidney function treated within the same period. All the patients were treatment naïve and had well compensated liver disease. The ESRD patients received 135 µg of PEGylated interferon α-2a (PegIFN-α) weekly and a reduced dose of ribavirin (RBV) was administered to 23/39 patients with an initial haemoglobin level > 10 g/dL. Control group patients were given standard doses of PegIFN-α and RBV. SVR was assessed as HCV RNA negativity 24 wk post-treatment. A t-test or ANOVA were used for comparisons of the means and a χ² test.
compared the frequencies. Logistic regression was used to determine significant predictors of SVR. Cutoff values for continuous variables were obtained from Receiver Operating Characteristic analysis.

RESULTS: The distribution of IL28B rs12979860 CC, CT and TT genotypes in the ESRD group was 28.2%, 64.1% and 7.7%, respectively, and 19.3%, 62.4% and 18.3% in the controls. The IFNL4 genotype was in almost absolute linkage disequilibrium with IL28B. The proportion of patients with a low ILV (< 600000 IU/mL) was significantly higher in the ESRD group than in the controls (28/39, 71.8% vs 51/109, 46.8%, \(P = 0.009\)), as was the proportion of patients with low ILV in IL28B CC carriers with compared with non-CC carriers in the ESRD group (10/11, 90.9% vs 18/28, 64.3%, \(P = 0.0035\)). This difference was not found in the controls (7/22, 31.8% vs 44/87, 50.6%, \(P = 0.9\)). The overall SVR rate was 64.1% (25/39) in the ESRD group and 50.5% (55/109) in the control group (\(P = 0.19\)). 11/11 (100%) and 19/22 (86.4%) IL28B CC patients achieved SVR in the ESRD and control groups, respectively. A statistically significant association between SVR and IL28B and IFNL4 variants was found in both groups. The ESRD patients who achieved SVR showed the lowest ILV [median 21000, interquartile range (IQR): 6000-23000 IU/mL], compared with ESRD individuals without SVR (1680000, IQR: 481000-6880000, \(P = 0.001\)), controls with SVR (387000, IQR: 111000-1253000) and controls without SVR (905000, IQR: 451000-3020000). In ESRD, an ILV < 600000 IU/mL was strongly associated with viraemia below this threshold.

CONCLUSION: Haemodialysis decreases the viral load, especially in IL28B CC genotype carriers. A low ILV was the strongest predictor of SVR in ESRD patients identified in multivariate analysis.

Key words: End-stage renal disease; Hepatitis C virus genotype 1; Interferon alpha; IFNL4; Ribavirin

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Core tip: The proportion of haemodialysed patients infected with chronic hepatitis C virus (HCV) receiving antiviral treatment remains unsatisfactory and should increase. Patients should be selected with high probability of successful treatment. Therefore, this study evaluated predictors of sustained virological response (SVR) in haemodialysed patients treated with PEGylated interferon \(\alpha\) for HCV genotype 1. The results of the study indicated that there was a high number of individuals with a low initial viral load (< 600000 IU/mL) among haemodialysed patients, especially in IL28B CC genotype carriers. A low initial viral load was the strongest predictor of SVR in haemodialysed patients.

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INTRODUCTION

The 10-year survival of kidney transplant recipients with hepatitis C (HCV) is significantly worse compared with non-infected patients\(^{(1)}\). Therefore, HCV eradication should be a standard procedure in HCV-infected patients considered for a kidney transplant. The reason to treat before kidney transplantation is supported by the fact that there is no effective and safe treatment in kidney transplant recipients. The use of interferon alpha in transplanted patients is considered controversial because of the high risk of interferon-induced kidney allograft dysfunction\(^{(2)}\). Furthermore, antiviral treatment should be also considered in all HCV-infected end-stage renal disease patients (ESRD) patients, because of their increased all-causes mortality when on maintenance haemodialysis\(^{(3,4)}\). Despite the negative impact of HCV infection on the life expectancy of patients on maintenance haemodialysis, most of the patients remain untreated. The epidemiological study published by Goodkin et al\(^{(5)}\) showed that only 1% of HCV-infected patients were given antiviral therapy. The treatment rate was higher in the group of patients enlisted for kidney transplantation, but was still only 3.7%. The reason for treatment deferral is undoubtedly the burden of interferon alpha therapy, long treatment duration and postponement of kidney transplantation\(^{(6-10)}\).

The proportion of haemodialysed patients receiving antiviral treatment is expected to increase and an accurate predictor of sustained virological response (SVR) would be helpful in the treatment decision algorithm. A treatment that significantly postpones patients’ enlistment should be proposed, especially to individuals who have a high probability of SVR, i.e., HCV eradication. The SVR rate is significantly better in non-genotype 1 infected patients than in genotype 1 patients, who are in general considered to be difficult-to-treat. Therefore, identification of the subset of easy-to-treat patients among those with genotype 1 is important to reliably select individuals with high probability of SVR.

In patients with normal kidney function, the IL28B rs12979860 genotype (a generally used marker of the functional IFNL4 ss469415590 genotype, which is responsible for genetic predisposition to SVR\(^{(11)}\)), degree of liver fibrosis and low initial HCV RNA levels represent the most reliable pretreatment predictors of SVR in PEGylated interferon \(\alpha\) (PegIFN-\(\alpha\)) and RBV therapy\(^{(12-14)}\). Alterations of the innate immunity caused
by haemodialysis could modify the eradication process of HCV and change the predictive value of the above-described factors. A low IVL as a predictive factor of SVR in haemodialysed patients has been described in the meta-analysis published by Gordon et al[15]. This meta-analysis included all HCV genotypes and was not specific for genotype 1. Furthermore, the predictive value of the IL28B genotype has not been evaluated so far in haemodialysed patients.

The aim of our study was to assess and validate reliability of the standard predictive factors in genotype 1 patients with ESRD on maintenance haemodialysis.

**MATERIALS AND METHODS**

**Cases**

We evaluated 39 kidney transplant candidates with ESRD on maintenance haemodialysis, treated for chronic HCV infection in three outpatient speciality clinics in the Czech Republic, from January 2004 to October 2012. The cohort consisted of 24 males and 15 females of average age 52 years (range: 25-69). All patients were haemodialysed for at least 3 mo, three times per week. The mean duration of haemodialysis was 3 years (range: 1-19 years). Twenty-nine patients resumed maintenance haemodialysis after having undergone kidney transplant in the past with subsequent graft failure. All patients were Caucasian, HCV treatment-naïve, and infected with HCV genotype 1b.

Pretreatment liver biopsy was performed in 29 ESRD patients, nine of whom had fibrosis stage F3 or F4, according to the Metavir score, and 20 patients had stage F0-F2. All patients had compensated liver disease with no signs of proteosynthetic dysfunction (normal albumin, bilirubin and prothrombin time values), ascites or encephalopathy. Patients with a history of liver disease decompensation, HBV or HIV co-infection, and patients receiving any immunosuppressive or immunomodulation therapy at the time of treatment initiation, were excluded from the evaluation.

All patients were treated with PegIFN-α2a (40 kDa) at a reduced dose of 135 µg, administered subcutaneously once weekly after a haemodialysis session. Twenty-three patients (59%) with a haemoglobin level > 10 g/dL at baseline were concurrently treated with RBV at reduced dose, 200-400 mg weekly. Erythropoetin was used in patients with a haemoglobin level < 12 g/dL. The anticipated duration of treatment was 48 wk. SVR was assessed as HCV RNA negativity 24 wk post-treatment.

**Controls**

The control group consisted of 109 treatment-naïve Caucasian patients (54 males and 55 females) of average age 46 years, with chronic hepatitis C, genotype 1b. These patients were treated within the same period with once weekly subcutaneously administered PegIFN-α2a (40 kDa) at a dose of 180 µg, together with weight-adjusted RBV 1000-1200 mg daily. The anticipated treatment duration was 24 wk for patients with low pretreatment viraemia who achieved rapid virological response (RVR, i.e., negative HCV RNA at week 4 of treatment), and 48 wk for patients who had had high pretreatment viraemia or had not achieved RVR. SVR was assessed as HCV RNA negativity 24 wk post-treatment. All controls had normal renal function, estimated as glomerular filtration rate calculated using Cockcroft-Gault formula at baseline. Pretreatment liver biopsy was performed in 101 patients, of whom 49 had fibrosis F0-F2 and 52 had fibrosis score ≥ F3, according to the Metavir score.

**HCV RNA assessment**

HCV RNA was assessed accordingly to the period of treatment by the Roche AmpliPrep/COBAS® TaqMan® HCV Test v1.0 or v2.0 (Roche Molecular Systems, Branchburg, NJ, United States). Serum HCV RNA levels were determined at baseline, at weeks 4, 12, 24, 36, 48 of treatment and 12 and 24 wk after the end of therapy.

**IL28B and IFNL4 genotyping**

Patients were genotyped for IL28B rs12979860 C/T polymorphism by polymerase chain reaction, based on a restriction fragment length polymorphism assay, as described by Fabris et al[16]. To minimise genotyping errors, blank controls wells were left on the PCR plates and two operators, unaware of the status of the sample, performed the genotype assignment independently. Genotyping for the IFNL4 ss469415590 TT/ΔG polymorphism was performed by the custom TaqMan genotyping assay described in[17]. Written informed consent for DNA sampling was obtained from all patients and the study conformed to the declaration of Helsinki Ethical Guidelines.

**Statistical analysis**

Data are presented as means and standard deviations, medians and ranges or as frequencies, as appropriate. A t-test or ANOVA with Dunnet’s post hoc test was used for comparisons of the means and the χ² test was used to compare frequencies. Logistic regression was used to determine significant predictors of SVR. Cutoff points for continuous variables were obtained from Receiver Operating Characteristic (ROC) analysis. A P value < 0.05 was considered statistically significant throughout the study. Statistical analysis was performed using the SPSS 13.0 software.

**RESULTS**

**Demographic and treatment data**

Compared with patients with maintained renal function, ESRD patients were significantly older, had
lower baseline ALT activity, significantly lower initial HCV viral load (IVL) and achieved higher rate of early virological response (EVR). There were no statistically significant differences between the groups in terms of gender distribution, BMI, diabetes, Metavir fibrosis stage, and IL28B and IFNL4 genotypes (Table 1).

Of the 39 ESRD patients, 25 (64%) completed the entire course of treatment. In 8 patients (21%), the treatment was discontinued at week 12 or 24 because of lack of virological response, and in six patients (15%) because of severe adverse events (SAE). In the control group, 65 (60%) patients completed the entire course of treatment. The treatment was discontinued in 34 patients (31%) because of lack of virological response and in 10 patients (9%) because of SAE. The rate of treatment discontinuation did not differ significantly between groups. Six (15%) ESRD patients discontinued the treatment because of an SAE: non-functional renal allograft rejection (two patients), thrombocytopenia with bleeding complications (two patients), interferon-induced autoimmune hepatitis (one patient) and pneumonia (one patient).

Nevertheless, five out of these six patients with SAE achieved SVR. Concerning further adverse events, nine patients presented with worsening of anaemia requiring erythropoietin therapy (eight patients) or transfusion (one patient). One patient developed pancytopenia and one patient presented with respiratory infection requiring antibiotic therapy. In three patients, the dose of PegIFN-α1b had to be reduced to 90 µg because of adverse events.

### Initial viral load, IL28B and IFNL4 genotypes and treatment efficacy

**ESRD group:** The distribution of IL28B rs12979860 genotypes was CC 28.2%, CT 64.1%, TT 7.7%. The frequencies of the corresponding IFNL4 rs469415590 genotypes TT/TT, TT/ΔG and ΔG/ΔG were exactly the same, reflecting the strong linkage disequilibrium between the two loci. The percentage of patients with a low IVL (< 600000 IU/mL) was significantly higher in the ESRD group than in the controls (28/39, 71.8% vs 51/109, 46.8%, P = 0.009) as well as the percentage of patients with a low IVL in IL28B CC carriers compared with non-CC carriers in the ESRD group (10/11, 90.9% vs 18/28, 64.3%, P = 0.0035). This difference was not found in the controls (7/22, 31.8% vs 44/87, 50.6%, P = 0.9). The overall SVR rate was 64.1% (25/39). All CC patients, including one patient with a high IVL, achieved SVR. In contrast, only 50.0% (14/28) of non-CC patients achieved SVR (Table 2). All of them had a low IVL. The SVR rate in non-CC patients with a low IVL was 77.7% (14/18). In the subgroup of non-CC patients without SVR, there were only 4/14 (28.6%) with a low IVL. The CC genotype carriers, regardless of their IVL, and non-CC genotype carriers with a low IVL were easy-to-treat, with an overall SVR rate of 86.2% (25/29) (Table 2). The SVR rate in the ESRD patients treated with both PegIFN-α/β and RBV was 73.9% (17/23). Patients treated with PegIFN-α1b monotherapy achieved SVR only in 50.0% (8/16), but the difference was not significant (P = 0.126).

The SVR rate was 60.0% (12/20) in ESRD patients with pretreatment liver fibrosis stage F0-F2, 66.7%...
A high percentage of individuals with low viraemia among HCV-infected patients on maintenance therapy.
Hemodialysis has already been reported, and two different hypotheses explaining low viraemia have been postulated. The first hypothesis is based on the adsorption of the virus on the haemodialysis membrane \(^{17-19}\). Accordingly, HCV RNA and HCV Ag decreases were observed during the hemodialysis session \(^{20}\), but the adsorption activity was proved only when using the polysulphone membrane, not the cuprophan membrane \(^{18}\). The second hypothesis explains viraemia fluctuations by the immune mediated effect of increased levels of interferon-alpha during haemodialysis. Badalementi et al \(^{21}\) described an HCV RNA decrease and the reciprocal interferon-alpha blood level increase during the haemodialysis sessions. Activation of the interferon-alpha pathway during haemodialysis procedure may represent the factor facilitating the mechanism of viral clearance in the patients on maintenance haemodialysis. This hypothesis is in accordance with our finding of significantly lower IVL in the IL28B CC carriers compared with IL28B non-CC carriers. IL28B CC genotype carriers are prone to a higher activation of interferon-sensitive genes compared with non-CC genotype carriers \(^{14}\). We speculated that in haemodialysed patients, the viral clearance mechanism is modified by the above-explained increase of interferon-alpha level together with the additional alterations in adaptive and innate immunity mechanisms described by Barbossa \(^{22}\). The low IVL, in our opinion, reflects the spontaneous effort of the immune system to clear the virus and the administration of PEG-IFN results in completion of the virus clearance process.

The efficacy of PegIFN-\(\alpha\) monotherapy, as well as PegIFN-\(\alpha\) and RBV combination described in previously published studies, varies widely. A recent review \(^{23}\) analysed 13 original papers assessing the results of interferon-based anti-HCV therapy in haemodialysed patients. The analysis included patients treated by PegIFN-\(\alpha\) monotherapy as well as patients to whom a reduced dose of RBV was administered. The SVR rate ranged from 27.3% to 78.8%, and was further increased by co-treatment with RBV. Similar conclusions were drawn in the review by Fabrizi \(^{24}\): the SVR rate ranged between 12.5% and 56% in nine studies with PegIFN-\(\alpha\) monotherapy and between 29% and 97% in 7 studies assessing combined PegIFN-\(\alpha\) and RBV therapy. The superiority of PegIFN-\(\alpha\) and RBV

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**Figure 1** Initial viral load in end stage renal disease patients and controls grouped according to their IL28B genotype and sustained virological response. The data from 39 patients with end-stage renal disease and 109 controls are shown as individual dots. Horizontal bars indicate median (thick line) and interquartile range (thin lines). A Mann-Whitney test was used to compare the means. End stage renal disease (ESRD) patients had significantly lower initial viral load (IVL) than controls (A). IL28B CC carriers had significantly lower IVL in the ESRD group, but not in the control group (B). Low IVL predicted better a sustained virological response (SVR) in the ESRD group (C) than in controls (D).
combination to PegIFN-α monotherapy has recently been documented in two prospective comparative studies; however, other predictors of SVR have not been assessed \[24,25\]. Our ESRD patients, who were treated with the PegIFN-α and RBV combination, also achieved a better SVR rate than the patients treated with PegIFN-α monotherapy. However, there was no significant difference because of the small number of patients included in the PegIFN-α monotherapy group.

The reason for the large variation in SVR rate may lie in variable ratios of genotype 1 to non-1 patients, and different percentages of patients with low viraemia in the published studies.

In our group, consisting solely of genotype 1b patients, we achieved a satisfactory SVR rate despite the fact that RBV was administered only to 23 out of the 39 treated patients. The high proportion of patients with low viral load in our group represented a factor that also increased the overall SVR rate in our ESRD cohort (IVL < 600000 IU/mL in 28/39, i.e., 71.8%). Our data are comparable with a recently published paper by Wang et al\[26\], in which the authors described 16 genotype 1b infected patients on maintenance hemodialysis treated with PegIFN-α monotherapy. Twelve of the 16 patients had low IVL and 11/12 achieved SVR.

We concluded that genotype 1 patients with ESRD should not be considered generally as difficult-to-treat, because in this group, patients with high probability of SVR achievement can be identified. In ESRD patients with genotype 1, SVR is predictable based on the same pretreatment variables as in patients with normal renal function. Patients with a high probability of SVR achievement can be identified according to low IVL and their IFNL4 genotype. Identically to patients with normal renal function, the prediction based on IFNL4 genotype testing in Europeans is not superior to IL28B genotype assessment in ESRD patients. The treatment-decision process, i.e., to treat immediately or to defer treatment and transplant with HCV infection waiting for the new treatment options, should also take into consideration overall life expectancy, comorbidities and the estimated risk of adverse events during therapy.

![](image_url)
Membranous glomerulonephritis associated with hepatitis C virus infection in renal transplant patients. Transplantation 1997; 63: 1634-1639 [PMID: 9197359 DOI: 10.1097/00007890-199706150-00017]

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