Brief Report

Pegylated interferon alfa-2a (40 kD) and ribavirin in haemodialysis patients with chronic hepatitis C


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Abstract

Background. Chronic hepatitis C virus (HCV) infection is associated with liver dysfunction and hepatocellular carcinoma. In patients with normal kidney function, treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) frequently leads to eradication of HCV. Treatment in dialysis patients has long been controversial and until recently, the use of RBV was considered to be contra-indicated. We used plasma trough levels of RBV to promote tolerance, safety and efficacy. PEG-IFN alfa-2a (40 kD) was chosen because it is cleared predominantly via hepatic metabolism.

Methods. Seven haemodialysis patients with chronic HCV infection were eligible and started with 135 µg PEG-IFN alfa-2a (40 kD) weekly and 200 mg RBV every other day. Dose adaptations were allowed following study guidelines. Genotypes 1 and 4 (five patients) were treated for 48 weeks and genotypes 2 and 3 (two patients) for 24 weeks. HCV-RNA was determined after 12, 24 and 48 weeks (and at 72 weeks for genotypes 1 and 4). RBV trough plasma levels were monitored regularly by HPLC-technique.

Results. All patients completed the treatment. In two patients, the PEG-IFN dose had to be reduced to 90 µg/week because of adverse events. To achieve the target range (1.5–2.5 µg/ml) of the plasma trough level, the mean RBV dose was increased to a dose between 133 and 200 mg each day in five patients. Despite an increase of the weekly erythropoietin (Epo) dose, two to a max of four red cell transfusions were given to four patients. A sustained viral response (SVR) was reached in five patients (3/5 with genotype 1/4 and 2/2 with genotype 2/3).

Conclusion. In our series of seven patients, we were able to use RBV monitoring drug levels in combination with PEG-IFN alfa-2a (40 kD) and achieve high sustained response rates. However, Epo and transfusion requirements may increase. Two patients adverse events were observed, but manageable with dose reduction of PEG-IFN.

Keywords: end-stage renal disease; HCV infection; pegylated interferon; ribavirin; sustained viral response

Introduction

ESRD patients with chronic HCV infection have an increased rate of mortality due to cirrhosis and hepatocellular carcinoma. This is already significant 6 years after the start of dialysis [1–3]. Again, after kidney transplantation a diminished graft and patient survival is found within 10 years. Activation of viral replication under the influence of immunosuppressive therapy certainly plays a role in the HCV-associated glomerulonephritis of the graft [4–7]. Several authors have suggested eradicating HCV infection [4,6–8] and advise to try this before transplantation because interferon (IFN) can promote graft dysfunction [9]. Once HCV is eradicated, this result is durable in 90–100% after kidney transplantation [10,11].

Standard IFN monotherapy was used in many studies. The percentage of sustained viral response (SVR) (37–40%) is better than in patients with normal kidney function (6–18%) possibly because higher blood levels are reached and because the immune response is improved. Many adverse events, a high drop-out rate and still low efficacy make this treatment unattractive in ESRD patients [11,12].

Some studies have shown that PEG-IFN alfa-2a can be used safely in dialysis patients [11,13], and with fairly good results [14–16]. We found that ribavirin (RBV) combined with standard IFN had to be given in a very low dose (100–200 mg/day) to avoid serious side effects [17]. RBV is cleared to a great extent by the kidney and accumulates in renal insufficiency with haemolytic anaemia as a serious side effect. Its use was considered to be contra-indicated.
Table 1. Overview of viral response to PEG-IFN/RBV combination therapy

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (year)</th>
<th>Genotype</th>
<th>Initial HCV-RNA a (copies/ml)</th>
<th>End of treatment</th>
<th>24 weeks after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>35</td>
<td>1b</td>
<td>461 000</td>
<td>Neg. (48 weeks)</td>
<td>11 000 copies/ml</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>31</td>
<td>1b</td>
<td>403 000</td>
<td>Neg. (48 weeks)</td>
<td>SVR</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>47</td>
<td>4c/d</td>
<td>766 000</td>
<td>Neg. (48 weeks)</td>
<td>7600 copies/ml</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>38</td>
<td>1a</td>
<td>450 000</td>
<td>SVR</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>46</td>
<td>1b</td>
<td>1 290 000</td>
<td>SVR</td>
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<tr>
<td>6</td>
<td>M</td>
<td>37</td>
<td>3a</td>
<td>736 000</td>
<td>SVR</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>46</td>
<td>2a</td>
<td>3 170 000</td>
<td>SVR</td>
<td></td>
</tr>
</tbody>
</table>

aBranch DNA technique.

bPCR technique.

cSVR = sustained viral response.

in ESRD patients, but today more experience in a combination with PEG-IFN alfa-2a has been published. A reduced dose combined with an increased erythropoietin (Epo) dose can limit anaemia, but careful clinical and haematological follow-up is necessary [18–20].

We chose PEG-IFN alfa-2a because it offers best results in combination with RBV [21], but also because it is cleared predominantly by hepatic metabolism [13,22]. A dose of 135 µg/week is advised because the clearance is still reduced by about 25% [13].

Patients and methods

Stable patients, aged >18 years on regular haemodialysis for at least 1 year were eligible. The HCV-RNA-PCR test had to be positive repeatedly within a period of at least 1 year before starting treatment. Treating physicians could bring candidates to our attention after consulting detailed guidelines published on the website of the Dutch Federation of Nephrology (NFN). If a patient was considered for treatment following our guidelines, this could only happen after we had ascertained that a candidate met all inclusion and exclusion criteria. The physician caring for the patient accepted to offer all results for centralized reviewing. No patients were excluded and all included patients were reported.

Important exclusion criteria were: concomitant hepatitis B or HIV-infection, signs of cirrhosis or liver cell insufficiency, haemoglobin level <8.5 g/dl, white blood cell count <2000/mm³, platelet count <90 000/mm³, psychiatric disorders, alcohol or drug abuse, concomitant auto immune disease, severe chronic obstructive lung disease and uncontrolled hypertension. A negative pregnancy test and effective contraception during the study period were required for women of childbearing age. A liver biopsy was not obligatory.

Seven caucasian patients (all candidates for kidney transplantation) were included. The pre-treatment dialysis periods ranged from 1.5 to 10.6 years. The main patient characteristics, the initial quantitative viral load and genotypes are mentioned in Table 1. The diagnosis of kidney disease was unknown in cases 3, 4 and 5. The other diagnoses were chronic glomerulonephritis, hypertensive nephropathy, chronic pyelonephritis and membranoproliferative glomerulonephritis in cases 1, 2, 6 and 7, respectively.

Treatment schedule

All patients started with 135 µg PEG-IFN alfa-2a (40 kD) (Pegasys®) s.c. once weekly, administered at the end of a dialysis session. RBV (Copegus®) was initially dosed with one capsule of 200 mg every 48 h.

Discontinuation or stepwise dose reduction of PEG-IFN was left to the judgement of the treating physician using clinical, haematological and biochemical parameters from the product information (SPC). The only change that was made concerned the reduction of the RBV dose. This was indicated by adverse events that could not be solved otherwise, a haemoglobin value <8.0 g/dl or a plasma level of RBV exceeding the therapeutic range (1.5–2.5 µg/ml). A stepwise increase of the dose was only indicated by a trough level below this range. HCV genotypes 1/4 were treated 48 weeks and genotypes 2/3 received a course of 24 weeks. Physicians were advised to bring the Hb level to a target of 11.2 g/dl for women and 12.1 g/dl for men, by increasing the Epo dose before the start of antiviral treatment.

Laboratory monitoring

RBV plasma trough levels were measured by the high performance liquid chromatography (HPLC) technique. The samples were taken just before a dialysis session and ≥24 h after the last capsule at 2, 4, 8, 12, 16 and 24 weeks. This was also done at 28, 38 and 48 weeks in genotype 1/4. Monitoring of HCV-RNA (Cobas Amplicor-HCV test version 2.0, lower limit of detection 50 copies/ml) was done at baseline and at 12, 24, 48 and 72 weeks. Laboratory checks of Hb, WBC, platelets, ALT and AST were made each fortnight till Week 20 and thereafter each 4 weeks till Week 28. Depending on the duration of treatment, these checks were repeated at Weeks 34, 48, 60 and 72. Glucose and TSH levels were also monitored and in each patient an ECG registration and ultrasound of the upper abdomen was made before the start of treatment.

Results

HCV-RNA monitoring

All patients completed the treatment and were observed at least 6 months thereafter. At 12 weeks, five patients were
Pegylated IFN alfa-2a and ribavirin therapy in ESRD patients

Table 2. Evolution of Hb level, RBV dose and Epo dose during treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Level/dose</th>
<th>0 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>16 weeks</th>
<th>20 weeks</th>
<th>24 weeks</th>
<th>28 weeks</th>
<th>38 weeks</th>
<th>48 weeks</th>
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<tr>
<td></td>
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<td>100</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>300</td>
<td>200</td>
<td>100</td>
<td>100</td>
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<tr>
<td></td>
<td>Epo d</td>
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<td>8</td>
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<td>12</td>
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<td>12</td>
<td>16</td>
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<td>13.8</td>
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<tr>
<td>6a</td>
<td>Hb b</td>
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<td>10.1</td>
<td>9.8</td>
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<tr>
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<td>7a</td>
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<td>10.1</td>
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</tr>
<tr>
<td></td>
<td>Epo d</td>
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<td>8</td>
<td>12</td>
<td>16</td>
<td>16</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

*In these cases blood transfusions were given.

Table 3. Adverse events and PEG-INF-dose reduction

<table>
<thead>
<tr>
<th>Case</th>
<th>Adverse event</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Hypertension/oedema</td>
<td>Recovery after correction of dry weight by ultrafiltration. No reduction of PEG-IFN</td>
</tr>
<tr>
<td>4</td>
<td>Hypertension/oedema and visual disturbance at Week 12</td>
<td>Recovery after correction of dry weight and anti-hypertensive treatment. No reduction of PEG-IFN</td>
</tr>
<tr>
<td></td>
<td>Neutropenia (2.5 × 10⁹/l) and thrombocytopenia (38 × 10⁹/l) at Week 30*</td>
<td>Recovery after dose reduction to 90 µg/week</td>
</tr>
<tr>
<td>5</td>
<td>Loss of appetite, loss of body weight &gt;5%, change of mood*</td>
<td>Recovery after dose reduction to 90 µg/week</td>
</tr>
</tbody>
</table>

*Classified as adverse event.

Haemoglobin level and blood transfusion management

The evolution of the Hb level in the individual patients (in relation to the EPO dose and RBV dose) is shown in Table 2. The lower limit of the acceptable Hb level was defined as 8.0 g/dl. Only in case 6 a level of 7.7 g/dl was reached at one moment, whereupon two blood donations of two units each were given. Fatigue was the only reason to transfuse red cells in three other cases without ever reaching a critical Hb level (a maximum of four units in two of them).

Erythropoietin dose

At start the mean dose was 11 400 IU/week and the mean maximal increase was 7700 IU/week. The individual adaptations are shown in Table 2.

Side effects

Loss of appetite, fatigue and dry skin were observed in the majority of patients. The individual loss of dry weight (a well-known phenomenon in IFN treatment) ranged from 0.5 to 3.5 kg. An adequate estimate of this loss is essential because reduction of the IFN dose is necessary if it exceeds 5% of the initial weight. Furthermore, it is essential for an adequate regulation of the fluid balance (see Table 3).

Adverse events and dose reduction of PEG-IFN

All patients were able to continue with PEG-IFN treatment. Reduction of dose was applied in two patients for different reasons (see Table 3).
WBC count and platelet count
Lowering of the WBC and platelet counts was obvious. The trough levels during treatment were 3.0 ± 0.44 × 10^9/l and 85 ± 48 × 10^9/l, respectively (means ± SD, normal values WBC: 4.3–10.8 × 10^9/l and platelets: 130–400 × 10^9/l). A critical level was not reached in any patient, but in one patient (case 4) this was the reason to reduce the PEG-IFN dose (see Table 3).

Ribavirin trough level monitoring and dose adaptations
RBV was not discontinued in any patient. Individual dose adaptations were only made when the trough-level concentrations were below or above the defined range (1.5–2.5 µg/ml) in five patients, ending up with a dose between 100 and 200 mg/day in six patients (see Table 2). In one patient (case 3) 400 mg/day was given without any effect on the low trough levels, but his compliance with RBV was doubtful.

ECG and ultrasound registrations
ECG registrations did not show abnormalities. With ultrasound examination, there was no indication of hepatocellular carcinoma or portal hypertension, but in two patients the spleen was slightly enlarged (length 14.3 and 14.0 cm, respectively) and in one patient the liver was enlarged (liver span 17 cm).

Liver function tests
Normal or slightly elevated levels of AST and ALT were noted on screening and during therapy.

Histology
In five patients, a liver biopsy was performed before the start of treatment. There were no signs of cirrhosis, the Metavir score was as follows: case 1: F0-A1, case 2: F0-A2, case 3: F1-A2, case 6: F1-A1, case 7: F2-A2. In this score the ‘F’ codes for fibrosis (five grades) and the ‘A’ codes for activity (four grades).

Discussion
Dialysis patients are a vulnerable population, often with hidden comorbidity; treatment of HCV-infection may have intolerable side effects, and is therefore controversial. In patients with normal kidney function much progress has been made and treatment is widely accepted.

As addition of RBV to PEG-IFN adds significantly to the efficacy of antiviral treatment [21], it is desirable to explore its possibilities also in dialysis patients. In the introduction we explained why especially PEG-IFN, alfa-2a is attractive for this group. Although RBV was considered to be contraindicated, it has now been shown that it can be used in dialysis patients if given in a low dose (100–200 mg/day) and in combination with a high dose of Epo [19,20]. During revision of our manuscript, a paper of Rendina et al. was published that also showed a very good efficacy, tolerability and safety of RBV in combination with PEG-IFN alfa-2a [20].

We decided to start RBV in a dose of 200 mg/48 h, together with an increased dose of Epo, but added frequent RBV trough level determinations to keep the level within a defined therapeutic range [23–25]. Below 1.5 µg/ml efficacy of RBV decreases and above 2.5 µg/ml toxicity increases together with efficacy. The upper limit is a compromise between efficacy and toxicity. Therefore plasma level determinations may improve efficacy and safety by avoiding adverse drug reactions. In six of our seven patients, the Epo dose remained far below 30 000–40 000 IU/week as advised in recent studies and in four of them blood donations were given [19,20]. Possibly these donations could have been prevented by a more generous use of Epo. Discontinuation of RBV can be prevented as shown in our patients and in the literature [19,20]. This is important for preservation of efficacy.

PEG-IFN-related adverse events were observed in two of our patients, but could be managed. Although a clinical significant event was not reached, a dose reduction because of neutropenia and thrombocytopenia was applied following the guidelines in case 4. Loss of weight (>5%) and change of mood were reasons to reduce the dose in case 5. Both reductions to 90 µg/week were followed by a SVR.

In two other situations (cases 2 and 4) with oedema and hypertension, correction of dry body weight and an antihypertensive drug in one of them was enough for complete recovery, without reduction of the PEG-IFN dose.

In our patients, the dosing of RBV was almost entirely based on trough levels. Because RBV is a slow reacting drug and more equilibrium time is required, a turnaround time of less than 2 weeks is not useful. Frequent sampling (each 2–3 weeks) is only necessary the first 8–12 weeks, whereafter the levels tend to stabilize and sampling can be individualized to once in 4–8 weeks.

The outcome of our treatment was successful in five of seven patients (SVR in 71.5%) and this is comparable with the results in patients with normal kidney function. This small study provides pilot data supporting the design of a large clinical trial using RBV and monitor levels, with PEG-IFN in haemodialysis patients with hepatitis C. The extra costs were calculated at € 15 380 for a 48-weeks treatment. In spite of these costs, we believe that this treatment should be considered in transplantation candidates.

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Conflict of interest statement. None of the authors had involvements that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated.

References


13. Lamb MW, Marks IM, Modi MW et al. Peg interferon alfa-2a (40 kD) (Pegasys) can be administered safely in patients with end-stage renal disease (abstract). *Hepatology* 2001; 34: 326


22. Modi MW, Fulton JS, Buckmann DK et al. Clearance of pegylated (40 kD) interferon alfa-2a (Pegasys®) is primarily hepatic. *Hepatology* 2000; 32: 371A


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