Mini Review

Treatment of Hepatitis C Virus Infection in Patients with End-Stage Renal Disease: Progress and Challenges

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Abstract

Hepatitis C virus (HCV) infection is a major health problem in patients with end-stage renal disease (ESRD). The incidence of acute HCV infection during maintenance dialysis is much higher than that in the general population due to nosocomial transmission. Following acute HCV infection, most patients remain viremic and evolve into chronic infection, leading to chronic hepatitis, cirrhosis, and even hepatocellular carcinoma (HCC). Overall, ESRD patients with chronic hepatitis C (CHC) have an increased risk of liver-related morbidity and mortality, either on maintenance dialysis or after renal transplantation (RT). Interferon (IFN) therapy is modestly effective for HCV infection in ESRD patients. Conventional or pegylated IFN monotherapy has been employed to treat acute hepatitis C (AHC) in ESRD patients with excellent safety and efficacy. Regarding CHC, approximately one third of the patients can achieve sustained virological response (SVR) by conventional or pegylated IFN monotherapy. The introduction of low-dose ribavirin in combination with conventional or pegylated IFN has further improved the SVR rate in treatment-naïve or treatment-experienced patients. Similar to HCV-infected patients with normal renal function, baseline viral load, viral genotypes, and on-treatment viral decline are useful for guiding therapy in ESRD patients. Of particular note, IFN-based therapy is not recommended for viremic patients who receive RT because of the low SVR rate and the high risk of acute graft rejection. In conclusion, ESRD patients with HCV infection should be encouraged to receive antiviral therapy. Treated patients who achieve SVR usually have long-term durable virological, biochemical, and histological responses.

KEY WORDS: hepatitis C virus, end-stage renal disease, dialysis, interferon, ribavirin

Introduction

Despite the introduction of universal precautions, blood product screening, as well as the use of erythropoietin to reduce the need for blood transfusion, hepatitis C virus (HCV) infection still remains a major health problem in patients with end-stage renal disease (ESRD). It is estimated that the annual incidence rates of HCV infection in ESRD patients range from 0.2% to 6.2%, which are about 100-1,000 times higher than that in the general population (1-19). Once exposed to HCV infection, the patients have a mean incubation period of 8 weeks before the onset of symptoms. Although some patients may present non-specific symptoms, such as fatigue, anorexia, or abdominal discomfort during acute infection, most are asymptomatic with mildly to moderately elevated serum alanine aminotransferase (ALT) levels; with ALT values ranging from 2-20 times the upper limit of normal (ULN) (4, 20, 21). Diagnosing acute HCV infection in ESRD patients is usually confirmed by the documentation of anti-
HCV seroconversion and the detection of serum HCV RNA.

Without effective therapeutic interventions, about 65%-92% of ESRD patients with acute hepatitis C (AHC) will evolve into chronic hepatitis C (CHC) (2, 4, 20, 21). The high rates of acute infection and chronicity following acute infection in ESRD patients contribute to the high prevalence rates. The reported prevalence rates of chronic HCV infection among ESRD patients are from 3.4% to 80% with great geographic variation (2, 7, 10-12, 22-35). The higher incidence and prevalence rates of HCV infection among ESRD patients suggest the possible routes of nosocomial transmission, such as contamination of the hands of staff members, sharing items between patients, dialyzer reuse, and contamination of dialysis machines (36-40). ESRD patients with CHC usually have an apparent indolent clinical course with only mildly elevated serum ALT levels (41).

Natural History of HCV Infection in ESRD Patients

The natural history of ESRD patients with CHC remained elusive during the early years of HCV infection. This is because the morbidity and mortality rates in these patients are generally higher than those in the general population, thus making the long-term consequences of HCV infection difficult to clarify. However, several studies have shown that HCV-infected ESRD patients on maintenance dialysis are at increased risks of liver-related morbidity and mortality, compared with those without HCV infection (13, 26, 42-52). Furthermore, HCV infection decreases adversely the health-related quality of life (HRQOL) (53). Although ESRD patients with CHC who receive renal transplantation (RT) usually have a higher survival rate than those on maintenance dialysis, several studies indicate that these patients have poorer patient and graft survival after RT (54-61). Of particular note, these patients have accelerated hepatic fibrosis and necroinflammation after RT, suggesting that immunosuppression may worsen the liver-related outcomes following RT (62-65).

Diagnosis of HCV Infection in ESRD Patients

Biochemical Assays

Although the serum ALT level is widely employed to screen liver diseases in the general population, ESRD patients tend to have lower ALT levels (66, 67). Several studies have shown that the optimized cut-off ALT level for ESRD patients with CHC is about 0.4-0.45 times the ULN of conventional level (41, 68, 69).

Serological Assays

Currently, there are two types of anti-HCV assays for screening patients with HCV infection, namely the enzyme immunoassay (EIA) and the recombinant immunoblot assay (RIBA). The first-generation EIA (EIA-1) contained a single recombinant antigen in the HCV nonstructural region (NS4) and was limited by the high false-negative and false-positive rates. The subsequent assays (EIA-2 and EIA-3), which contain additional antigens in the core, NS3, NS4, and NS5 regions, further increase the sensitivity and specificity, and are therefore widely used in clinical practice. Although RIBA is considered reproducible and confirmative to diagnose HCV infection for positive EIA samples, it is rarely used after the introduction of highly sensitive molecular assays to detect the circulating HCV RNA.

In ESRD patients receiving maintenance dialysis, previous studies have shown that the false-negative rates of EIA-2 for diagnosis of HCV infection were 2.6-7.0%, with HCV RNA taken as the reference standard (40, 70). EIA-3 provided excellent accuracy, with 0-0.23% false-negative rates. Thus, EIA-3 is an effective screening tool for HCV infection in patients with ESRD (71, 72). In contrast, these assays may not discriminate patients with chronic HCV infection from patients with acute resolving HCV infection, or chronic HCV-infected patients with treatment-induced viral eradication. Using sensitive virological assays can help confirm the patients’ clinical status.

Virological Assays

HCV RNA is the direct marker of HCV replication, which can be employed to estimate the level of viral replication and to monitor the effectiveness of antiviral therapy. HCV RNA can be determined qualitatively or quantitatively using different molecular techniques. Furthermore, HCV genotype is the intrinsic characteristic of the infected HCV strains and remains stable during the course of chronic infection. Evaluation of HCV RNA and genotype can help evaluate the prognosis, and determine the optimal duration and dosage of interferon (IFN)-based therapy (73, 74).

Several studies have found that the HCV RNA level decreases transiently during hemodialysis and returns gradually to the baseline level within 48 hours (75-77). Adsorption of HCV onto the dialysis membrane, destruction of HCV particles, escape of HCV into the dialysate, and increased plasma IFN-α levels during dialysis are implicated in this phenomenon (78, 79). It is recommended that the viral load should be determined prior to each session of hemodialysis to avoid underestimation. Although the HCV genotype...
distribution varies widely among different geographic regions, HCV genotypes 1 and 2 predominate in ESRD patients with CHC (80-82).

**Histological Assays**

Currently, percutaneous liver biopsy is the gold standard for assessing the liver histology in ESRD patients with CHC, by which physicians can evaluate the eligibility for RT, the long-term prognosis, and the necessity for IFN-based therapy (83). Compared with non-uremic HCV patients, ESRD patients with CHC tend to have milder hepatic necroinflammation and fibrosis (84-86). Longer duration of infection, advanced age at infection, elevated serum aspartate aminotransferase (AST) and severe hepatic necroinflammation on liver biopsy are associated with significant hepatic fibrosis (86, 87).

However, liver biopsy is an invasive procedure, which is limited by poor patient acceptance, potentially serious bleeding events, and sampling errors (88-90). An accurate and readily available noninvasive test for ESRD patients with CHC is needed to predict the severity of liver histology. Two studies indicated that the AST-to-platelet ratio index (APRI), obtained with simple blood tests, was useful for predicting the severity of hepatic fibrosis in ESRD patients with CHC (91, 92). However, the major strength of APRI is to exclude patients with significant hepatic fibrosis (≥ F2, by METAVIR score) when the cut-off level is set at < 0.40; this saves at most 50% of correctly diagnosed patients. In recent years, liver stiffness measurements (LSMs) by transient elastography (TE, Fibroscan®) have been more accurate than APRI in estimating the severity of hepatic fibrosis in ESRD patients with CHC, and about 90% of the patients can be correctly diagnosed without the need of invasive biopsy (93).

**Definition of HCV Virological Response following Antiviral Therapy**

The goal of HCV treatment is to decrease patients’ liver-related morbidity and mortality. The evolution to end-stage liver disease (ESLD) in ESRD patients with CHC usually takes several decades; hence, it is difficult to show the beneficial effect of treatment in halting the liver-related complications. Sustained viral suppression rather than long-term clinical outcome is therefore defined as the surrogate endpoint of IFN-based therapy. The most important is sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after the completion of therapy by a sensitive HCV RNA assay. This endpoint is generally believed as a “virological cure”, according to the long-term follow-up data for patients who achieved SVR through antiviral therapy (94). The other non-SVR patients comprise relapsers (undetectable HCV RNA at the end of treatment, but detectable HCV RNA at the end of follow-up), patients with virological breakthrough (undetectable HCV RNA during treatment, but detectable HCV RNA at later treatment period), and non-responders (never reaching undetectable HCV RNA during treatment). Furthermore, the on-treatment viral declines during the first 12 weeks reflect the patients’ responsiveness to treatment. Rapid virological response (RVR) was defined as undetectable HCV RNA at week 4 of treatment; week-8 response (Wk-8R), defined as undetectable HCV RNA at week 8 of treatment in the absence of RVR; and early virological response (EVR), defined as undetectable HCV RNA (complete, cEVR) or ≥ 2 log reduction of HCV RNA at week 12 of treatment to the baseline viral titer (partial, pEVR) (95). All the on-treatment viral kinetics are predictive of SVR to antiviral therapy (95-98). Generally speaking, the earlier the serum HCV RNA levels become undetectable, the higher SVR rates can be achieved.

**Treatment of ESRD Patients with AHC**

**Conventional IFN α Monotherapy**

Conventional IFN α monotherapy has been employed successfully to treat non-uremic patients with AHC. Treatment with conventional IFN at a dosage of 3-6 million units (MU) three times per week for 4-24 weeks had an overall SVR rate of 32%-98% (99-101). In ESRD patients with AHC, the overall SVR rate in patients who received conventional IFN at a dosage of 3-10 MU three times weekly for 12-48 weeks was 26%-86%, which was higher than those without receiving therapy (5.6%-12.5%) (Table 1) (102-106). Furthermore, the overall treatment-related withdrawal rate was 0%-22%. Patients who received a higher dosage of IFN and had lower HCV E1/NS1 single-strand conformational polymorphism (SSCP) band number had a higher SVR rate (103, 106).

**Pegylated IFN α Monotherapy**

The use of pegylated IFN α-2b at a dosage of 1.0-1.66 µg/kg per week for 12-24 weeks had an overall SVR rate of 82%-95% in non-uremic patients with AHC (107, 108). However, few studies have been conducted to evaluate the safety and efficacy of pegylated IFN for ESRD patients with AHC. Engel et al. identified 32 ESRD patients with AHC, and 10 received pegylated IFN α-2b at a dosage of 1.0 µg/kg per week for 24 weeks. The SVR rate was 40% and one of the 10 treated patients died during treatment because of pneumonia and fistula formation (109). Liu et al. evaluated 35 such patients, all of whom received...
pegylated IFN α-2a at a dosage of 135 µg per week for 24 weeks. The SVR rate in the treated group was significantly higher than that in the non-treated historical controls (89% vs. 17%); and the treatment-related withdrawal rate was 5.7% (4). Patients who received more than 80% of the scheduled treatment dosage and duration had an SVR rate of 90%. In contrast, baseline ALT levels, HCV RNA levels and HCV genotype did not affect the overall SVR rate. A 16-week watchful HCV RNA surveillance rule after the onset of AHC is helpful for discriminating the necessity of pegylated IFN α monotherapy in this situation (4).

**Treatment of ESRD Patients with CHC**

**Interferon α Monotherapy**

The SVR and treatment-related withdrawal rates of conventional IFN α monotherapy at a dosage of 3-6 MU three times per week for 24-48 weeks are generally less than 20% and 5%-10% in non-uremic patients with CHC, respectively (99). Treatment of ESRD patients with CHC by conventional IFN α monotherapy at a dosage of 1-6 MU daily to three times per week for 12-48 weeks had an overall SVR rate of 20%-71%. Furthermore, the overall treatment-related withdrawal rate was 0%-53% (Table 2) (110-133). Four meta-analyses showed that about one third of ESRD patients with CHC receiving conventional IFN α monotherapy can achieve SVR (134-137). However, the corresponding treatment-related withdrawal rates ranged from 20%-30%. The higher SVR and treatment-related withdrawal rates in ESRD patients than those in non-uremic patients with conventional IFN α monotherapy may be attributed to the higher IFN serum concentrations due to the decreased renal clearance (138).

Low baseline HCV RNA level, mild liver histology, and treatment dosage of 3 MU for at least 6 months are predictive factors for SVR (117, 124, 139). Patients with RVR have high probability of achieving SVR. In contrast, those who fail to clear HCV RNA after 4-8 weeks of therapy have a low likelihood of achieving SVR (117, 128, 130, 139).

**Pegylated IFN α Monotherapy**

The SVR and treatment-related withdrawal rates of pegylated IFN α monotherapy (pegylated IFN α-2a at a dosage of 180 µg per week; pegylated IFN α-2b at a dosage of 0.5-1.5 µg/kg per week) for 48 weeks are 18%-39% and 3%-7% in non-uremic patients with CHC, respectively (140, 141). Two pharmacokinetic studies showed that the effective antiviral concentration in ESRD patients treated with pegylated IFN α-2a 135-180 µg per week or pegylated IFN α-2b 1.0 µg/kg per week was comparable with that in non-uremic patients treated with pegylated IFN α-2a 180 µg per week or pegylated IFN α-2b 1.5 µg/kg per week (142, 143). Treatment of ESRD patients with

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Antiviral Agent</th>
<th>Dose and Duration</th>
<th>Sustained Virologic Response (%)</th>
<th>Withdrawal Rate (%)</th>
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<tbody>
<tr>
<td>Süleymanlar, et al. (102)</td>
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<td>Al-Harbi, et al. (105)</td>
<td>9</td>
<td>IFN-α</td>
<td>10 MU daily for 3 weeks, and 3 MU three times weekly for 12 weeks</td>
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<tr>
<td>Rocha, et al. (106)</td>
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MU: million units
### Table 2. Efficacy and safety of conventional or pegylated interferon α monotherapy in ESRD patients with chronic hepatitis C

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Antiviral Agent</th>
<th>Dose and Duration</th>
<th>Sustained Virologic Response (%)</th>
<th>Withdrawal Rate (%)</th>
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<td></td>
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<td>5 MU three times per week for 12 weeks, and 5 MU per week for 12 weeks (n = 7)</td>
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<td>Kamar, et al. (112)</td>
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<td>IFN α</td>
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<tr>
<td>Ozdemir, et al. (113)</td>
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<td>IFN α</td>
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<td>IFN α</td>
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<td>34</td>
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### Table 2. (Continued)

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<tr>
<th>Study</th>
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<td>Pegylated IFN α-2a</td>
<td>180 µg per week for 48 weeks</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>Tan, et al. (158)</td>
<td>34</td>
<td>Pegylated IFN α-2b</td>
<td>0.5 µg/kg per week for 4 weeks, and 1.0 µg/kg per week for 20-44 weeks</td>
<td>50</td>
<td>33</td>
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<tr>
<td>Annichiarico, et al. (159)</td>
<td>8</td>
<td>Pegylated IFN α-2b</td>
<td>0.6-1.1 µg/kg per week for 24 weeks</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Amarapurkar, et al. (160)</td>
<td>6</td>
<td>Pegylated IFN α-2b</td>
<td>1.0 µg/kg per week for 24 weeks</td>
<td>50</td>
<td>NA</td>
</tr>
<tr>
<td>Giguere, et al. (161)</td>
<td>5</td>
<td>Pegylated IFN α-2b</td>
<td>1.0 µg/kg per week for 24 weeks</td>
<td>60</td>
<td>NA</td>
</tr>
<tr>
<td>Russo, et al. (162)</td>
<td>16</td>
<td>Pegylated IFN α-2b</td>
<td>1.0 µg/kg per week for 48 weeks (n = 9)</td>
<td>22</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5 µg/kg per week for 48 weeks (n = 7)</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Espinosa, et al. (153)</td>
<td>9</td>
<td>Pegylated IFN α-2b</td>
<td>1.5 µg/kg per week for 24 weeks</td>
<td>57</td>
<td>44</td>
</tr>
</tbody>
</table>

**Meta-analysis**

| Fabrizi, et al. (134)           | 269                | IFN α           | 1.5-6 MU daily to three times per week for 12-48 weeks | 37                              | 17                 |
| Russo, et al. (135)             | 213                | IFN α           | 3-5 MU three times per week for 24-48 weeks | 33                              | 30                 |
| Fabrizi, et al. (136)           | 529                | IFN α           | 1-6 MU daily to three times per week for 8-48 weeks | 39                              | 19                 |
| Gordon, et al. (137)            | 459                | IFN α           | 1-6 MU daily to three times per week for 16-48 weeks | 41                              | 26                 |
| Fabrizi, et al. (136)           | 116                | Pegylated IFN α | 135-180 µg per week for 48 weeks (α-2a) or 0.5-1.0 µg/kg per week for 48 weeks (α-2b) (n = 116) | 31                              | 27                 |
| Gordon, et al. (137)            | 87                 | Pegylated IFN α | 135-180 µg per week for 24-48 weeks (α-2a) or 0.5-1.0 µg/kg per week for 48 weeks (α-2b) (n = 87) | 37                              | 28                 |
| Fabrizi, et al. (163)           | 254                | Pegylated IFN α | 135-180 µg per week (α-2a) or 0.5-1.1 µg/kg per week for 24-48 weeks (α-2b) | 33                              | 23                 |

MU: million unit; NA: not available
CHC by pegylated IFN α-2a or α-2b monotherapy at a dosage of 90-180 µg or 0.5-1.1 µg/kg per week for 24-48 weeks had SVR rates of 0%-79%, and the treatment-related withdrawal rates of 0%-56% (Table 2) (117, 127, 144-162). Three meta-analyses showed that the SVR and treatment-related withdrawal rates in patients receiving pegylated IFN α were 31%-37% and 23-28%, which are comparable with those in patients receiving conventional IFN (136, 137, 163). Although patients who receive conventional or pegylated IFN have similar efficacy and safety according to the meta-analyses, one head-to-head randomized trial showed that the efficacy and safety in patients with pegylated IFN α-2a were superior to those with conventional IFN α-2a (117).

Similar to ESRD patients who receive conventional IFN α monotherapy, low baseline HCV RNA level, HCV non-1 genotype, and RVR are positive predictors for SVR in those receiving pegylated IFN α monotherapy (117, 154, 157).

**IFN α and Ribavirin Therapy**

Using ribavirin in combination with conventional IFN α improves greatly the SVR rates to 31%-43% in non-uremic patients with CHC (164, 165). Ribavirin is considered contraindicated for ESRD patients with CHC because of the potential risk of life-threatening hemolytic anemia. However, several pilot studies showed that using low-dose ribavirin (200 mg three times per week to daily 400 mg) to keep target concentration of 10-15 µmol/L in combination with conventional IFN and high-dose erythropoietin (20,000-30,000 IU per week) to treat such patients was feasible. The overall SVR and treatment-related withdrawal rates after 24-48 weeks of the combination therapy were 17%-63%, and 0%-33%, respectively (Table 3) (166-168). Although these studies showed that it might be safe to use low-dose ribavirin to treat ESRD patients with CHC, the attending physicians should closely monitor the hemoglobin levels after treatment, and should promptly reduce the ribavirin dosage as well as initiate high dose of erythropoietin once clinical significant anemia occurs.

**Pegylated IFN α and Ribavirin Therapy**

Combination therapy with pegylated IFN α and ribavirin has improved the SVR rate to 54%-63% and has been the current standard of care to treat non-uremic patients with CHC (169-171). Till now, several studies have assessed the efficacy and safety of pegylated IFN α plus low-dose ribavirin for ESRD patients with CHC (Table 3) (157, 161, 172-178). The overall SVR and treatment-related withdrawal rates after 24 (HCV genotype 2 or 3 patients) or 48 weeks (HCV genotype 1 or 4 patients) of combination therapy were 7%-97% and 0%-71%, respectively. In line with patients treated with conventional IFN α and ribavirin, these patients also needed high-dose erythropoietin (10,000-90,000 IU per week) to prevent severe anemia (179). Patients with HCV genotype 2 or 3 infection tended to have higher SVR rates than those with genotype 1 or 4 infection.

One meta-analysis showed that the overall SVR and treatment-related withdrawal rates were 56% and 22% in ESRD patients with CHC receiving pegylated IFN α and ribavirin therapy (179). The main causes for premature treatment cessation were anemia and heart failure. Therefore, high-dose erythropoietin was needed to maintain patient safety during combination therapy. Furthermore, recent evidence from a head-to-head randomized trial showed that the SVR rate in patients receiving combination therapy was significantly higher than that in patients receiving pegylated IFN α monotherapy.

**Retreatment for Prior Relapsers to IFN α Monotherapy**

Although the safety and efficacy of conventional or pegylated IFN α plus ribavirin in retreating non-uremic patients with CHC whose prior IFN α monotherapy fails are well established, only two studies have addressed this issue in ESRD patients. Djordjević et al. retreated 4 patients who relapsed to 12 weeks of conventional IFN α monotherapy at a dose of 3 MU three times per week by the same protocol for another 24 weeks. Despite all the patients having good viral suppression and tolerance during retreatment, none of these patients achieved SVR (120).

Liu et al. retreated 35 patients who relapsed from 24 weeks of conventional or pegylated IFN α monotherapy by pegylated IFN α-2a at a dosage of 135 µg per week and ribavirin at a dosage of 200 mg per day for 48 (HCV genotype 1) or 24 (HCV genotype 2) weeks (177). The overall SVR rate was 60%, and the SVR rate in HCV genotype 2 patients was superior to that in HCV genotype 1 patients (80% versus 52%). The treatment-related withdrawal rate was 17%. Twenty-six (74%) percent of patients had to receive erythropoietin at a mean dose of 15,000 IU per week to manage anemia during combination therapy. Low baseline HCV RNA and RVR were independent predictors for SVR. In line with the meta-analysis results, the efficacy and safety profiles for retreated patients were comparable with untreated patients (179).

**Treatment of ESRD Patients with HCV Infection following RT**

Treatment of HCV infection following RT is...
Table 3. Efficacy and safety of conventional or pegylated interferon α plus low dose ribavirin in ESRD patients with chronic hepatitis C

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Antiviral Agent</th>
<th>Dose and Duration</th>
<th>Sustained Virologic Response (%)</th>
<th>Withdrawal Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interferon plus ribavirin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruchfeld, et al. (157)</td>
<td>6</td>
<td>IFN α-2b + ribavirin</td>
<td>3 MU three times per week (IFN α-2b), and 200-400 mg/qd (ribavirin) 28 weeks</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Tan, et al. (158)</td>
<td>5</td>
<td>IFN α-2b + ribavirin</td>
<td>3 MU three times per week (IFN α-2b), and 200-600 mg/qd (ribavirin) 24 weeks</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>Mousa, et al. (159)</td>
<td>20</td>
<td>IFN α + ribavirin</td>
<td>3 MU (IFN α), and 200 mg (ribavirin) three times per week for 24 weeks (n = 9) 3 MU (IFN α), and 200 mg (ribavirin) three times per week for 48 weeks (n = 11)</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td><strong>Pegylated interferon plus ribavirin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruchfeld, et al. (172)</td>
<td>6</td>
<td>Pegylated IFN α-2a or α-2b + ribavirin</td>
<td>135 µg per week (pegylated IFN α-2a) or 50 µg per week (pegylated IFN α-2b), and 200-400 mg/qd (RBV) for 48 (genotype 1, 4) or 24 (genotype 2) weeks</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>Rendina, et al. (173)</td>
<td>35</td>
<td>Pegylated IFN α-2a + ribavirin</td>
<td>135 µg per week (pegylated IFN α-2a), and 200 mg/qd (RBV) for 48 (genotype 1) or 24 (genotype non-1) weeks</td>
<td>97</td>
<td>14</td>
</tr>
<tr>
<td>Carriero, et al. (174)</td>
<td>14</td>
<td>Pegylated IFN α-2a + ribavirin</td>
<td>135 µg per week (pegylated IFN α-2a), and 200 mg/qd (RBV) for 48 (genotype 1) or 24 (genotype 2, 3) weeks</td>
<td>29</td>
<td>71</td>
</tr>
<tr>
<td>van Leusen, et al. (175)</td>
<td>7</td>
<td>Pegylated IFN α-2a + ribavirin</td>
<td>135 µg per week (pegylated IFN α-2a) and 200 mg every other day (RBV) for 48 (genotype 1, 4) or 24 (genotype 2, 3) weeks</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>Hakim et al. (176)</td>
<td>15</td>
<td>Pegylated IFN α-2a + ribavirin</td>
<td>135 µg per week (pegylated IFN α-2a) and 200 mg weekly to three times per week (RBV) for 48 weeks</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>Liu, et al. (177)*</td>
<td>35</td>
<td>Pegylated IFN α-2a + ribavirin</td>
<td>135 µg per week (pegylated IFN α-2a), and 200 mg/qd (RBV) for 48 (genotype 1) or 24 (genotype 2) weeks</td>
<td>60</td>
<td>17</td>
</tr>
<tr>
<td>Deltenre, et al. (178)</td>
<td>32</td>
<td>Pegylated IFN α-2a + ribavirin</td>
<td>135 µg per week (pegylated IFN α-2a), and 600 or 1000 mg per week (RBV) for 48 (genotype 1, 4) or 24 (genotype 2, 3) weeks</td>
<td>50</td>
<td>19</td>
</tr>
<tr>
<td>Giguere, et al. (161)</td>
<td>17</td>
<td>Pegylated IFN α-2a or α-2b + ribavirin</td>
<td>135 µg per week (pegylated IFN α-2a) or 1.0 µg/kg per week (pegylated IFN α-2b), and 200 mg/qd (RBV) for 48 (genotype 1, 4) or 24 (genotype 2, 3) weeks</td>
<td>76</td>
<td>0</td>
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<tr>
<td>Liu, et al. (157)</td>
<td>103</td>
<td>Pegylated IFN α-2a + ribavirin</td>
<td>135 µg per week (pegylated IFN α-2a), and 200 mg/qd (RBV) for 48 (genotype 1)</td>
<td>64</td>
<td>7</td>
</tr>
<tr>
<td><strong>Meta-analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fabrizi, et al. (179)</td>
<td>111</td>
<td>Pegylated IFN α-2a + ribavirin</td>
<td>135 µg per week (pegylated IFN α-2a) or 50 µg per week (pegylated IFN α-2b), and 170 mg/qd to 200 mg three times per week (RBV)</td>
<td>56</td>
<td>22</td>
</tr>
</tbody>
</table>

MU: million unit; NA: not available
*Relapsers from prior IFN α monotherapy
currently limited by its unsatisfactory safety and efficacy. One meta-analysis evaluated 102 RT recipients with CHC who received conventional IFN α with or without ribavirin combination therapy. The overall SVR and treatment-related withdrawal rates were 18% and 35%, respectively (180). Furthermore, acute allograft rejection which resulted in graft dysfunction or graft loss was frequently associated with treatment interruption (56, 180-182). Although the use of ribavirin or amantadine monotherapy, and ribavirin plus amantadine combination therapy showed serum ALT improvement without detrimental effects on renal graft function, these regimens did not have any beneficial effect on viral suppression or liver histology (183-186). Therefore, IFN-based therapy should only be initiated in RT recipients under specific clinical conditions, such as fibrosing cholestatic hepatitis, when the risk of not treating HCV infection outweighs the risk of graft loss.

Long-Term Beneficial Outcome after IFN-Based Therapy

There are evidences that ESRD patients with acute or chronic HCV infection who achieve SVR have better liver histology and improved quality of life than those who fail to achieve SVR after IFN-based therapy (117, 129, 187, 188). Furthermore, the SVR patients have decreased progression rate on liver histology even after RT (187). Several studies have also shown that the SVR patients can maintain long-term undetectable serum HCV RNA and normalized ALT levels, either during maintenance dialysis or after RT (112, 113, 189).

Future Perspectives

In recent years, genome-wide association studies have shown that the single nucleotide polymorphisms (SNPs) near the interleukin 28B (IL28B) gene (rs12979860 and rs8099917), which is located on chromosome 19 and encodes IFN λ-3, are highly associated with improved early viral kinetics as well as treatment-induced viral clearance in non-uremic HCV patients (97, 98, 190-194). Furthermore, the SNPs near the inosine triphosphate pyrophosphatase (ITPA) gene (rs1127354 and rs7270101), which is located on chromosome 20, are associated with ribavirin-induced hemolytic anemia (195, 196). However, the role of IL28B and ITPA SNPs in identifying the treatment responses as well as the severity of anemia in ESRD patients with HCV infection who receive IFN α with or without ribavirin combination therapy remains unknown.

In view of the efficacy concerns about the IFN α monotherapy and the safety concerns about IFN α with ribavirin combination therapy, are there any new drugs available and suitable for ESRD patients with CHC? The recent breakthroughs on HCV molecular biology have shed new light for non-uremic HCV patients. Using direct acting antivirals (DAAs), which target on the HCV NS protein, has greatly improved the overall SVR rates either for treatment-naïve or treatment-experienced HCV patients. These agents may be used alone or in combination with IFN α or ribavirin (197-201). Currently, the first-generation DAAs, telaprevir and boceprevir, for treating HCV genotype 1 patients with high SVR rates have been approved by FDA (197-200). Although these new agents have potent antiviral effects, the optimal dosage and the potential adverse events for ESRD patients with CHC are largely unknown and needed to be confirmed in future clinical trials.

Conclusions

HCV infection still remains a major health problem which can cause substantial liver-related morbidity and mortality in patients with ESRD. Universal precautions against nosocomial blood-borne infections, routine ALT and anti-HCV surveillance should be strictly followed so as to prevent and detect early acute HCV infection. Conventional and pegylated IFN α monotherapy are both effective and safe for the treatment of ESRD patients with AHC. Watchful surveillance of serum HCV RNA level during the first 16 weeks of AHC can help avoid unnecessary therapy for patients with acute self-limiting hepatitis C.

About one third of ESRD patients with CHC treated with conventional or pegylated IFN α monotherapy achieve SVR. Combining low-dose ribavirin plus conventional or pegylated IFN α can further increase the SVR rates for treatment-naïve or relapsed (after conventional or pegylated IFN α monotherapy) ESRD patients with CHC. However, close monitoring of the hemoglobin level and the prompt use of high-dose erythropoietin are required to prevent severe anemia after combination therapy. Evaluating the pre-treatment serum HCV RNA level, HCV genotype and stage of hepatic fibrosis, as well as monitoring the on-treatment serum HCV RNA levels are recommended for guiding the optimal therapy.

IFN-based therapy is generally not recommended for treating HCV infection after RT because it may cause graft dysfunction or loss. The beneficial effects on sustained viral suppression, biochemical remission, histological improvement and quality of life can be maintained in patients with SVR. Combining the new host genetic markers, such as IL28B and ITPA SNPs, to predict patients’ responses and safety may contribute to more appropriate therapy. Furthermore, the introduction of DAAs for ESRD
patients with HCV infection may provide better therapeutic care in the near future. Large-scale and well-conducted studies are needed to answer these interesting and important issues.

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