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Ribavirin Combination Therapy of Chronic Hepatitis C Patients with End Stage Renal Disease: Review of Evidences on Efficacy and Safety

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Abstract

Background and Aims: Only few small studies have evaluated efficacy of ribavirin in combination with pegylated interferon or standard interferon in hemodialysis patients. In current review, we aim to determine the efficacy and safety of ribavirin-containing regimen in these patients.

Methods: Medline, Scopus, ISI web of knowledge and Proquest were searched for prospective studies of IFN and PEG-IFN combined with ribavirin in IFN-naive dialysis patients with chronic Hepatitis C infection. Reporting of HCV RNA results at least 6 months after treatment using a PCR assay was mandatory.

Results: From 17 relevant studies, six studies met our inclusion criteria. Because of high level of heterogeneity and low number of studies, we discarded meta-analysis. Two studies investigated standard interferon plus ribavirin. One reported 66% of Sustained Viral Response and zero treatment discontinuation. In contrast, another study reported just 16% of Sustained Viral Response and 33% of treatment discontinuation. Four studies investigated pegylated interferon plus ribavirin. One study reported amazing Sustained Viral Response rate of 97%, however, another study reported Sustained Viral Response rate of just 28.6% and treatment discontinuation rate of 71.4%. Other reported Sustained Viral Response and treatment discontinuation rates were 50%, 70% and 16%, respectively.

Conclusion: Individuals on dialysis with chronic hepatitis C who were treated with interferon or pegylated interferon plus ribavirin can have higher Sustained Viral Response rate than dialysis patients treated with interferon or pegylated interferon alone. Administration of ribavirin with close monitoring of CBC and serum ribavirin concentration can be safe.

Keywords: Ribavirin, End Stage Renal Disease, Dialysis, Interferon, Pegylated Interferon

Introduction

Hepatitis C virus (HCV) infection is a major cause of liver disease in patients undergoing hemodialysis (HD) and is associated with higher mortality. There is also large variety in seroprevalence of HCV in hemodialysis patients (1). The reported prevalence of HCV among the HD population has varied from 1.9 to 84.6% in different countries and even in different regions within one country (2-12). Nonetheless, globally, in the last decade, seroprevalence of HCV infection in these kinds of patients had diminishing trend reflecting a number of factors such as, broad use of recombinant erythropoietin and resultant

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screening of blood products, improvement of quality and quantity of hemodialysis unit staffs and adherence to the universal precautionary measures (2, 11, 13-27).

Screening of all HD patients and therapy to decrease the burden of infection can prevent new cases in HD setting (26). Success of antiviral therapy in the end stage renal disease (ESRD) has been determined by numerous clinical trials with rates of sustained virological response (SVR) comparable and even more than patients with normal renal function those who treated with IFN alone (28-30). At present, Pegylated interferon (PEG-INF) and Ribavirin (RBV) are considered as standard treatment in patients with normal renal function. Because of the lack of knowledge about adequate dosing, safety and fear of side-effects, i.e. severe anemia, the use of RBV in ESRD is contraindicated (31). RBV is not filtrated through hemodialysis filters, accumulate in serum, and cause can dose-related hemolysis (32); whereas, administration of low dose RBV is currently evolving. Few handful small studies have evaluated efficacy of PEG-IFN or standard IFN combined with RBV in dialysis patients with chronic HCV infection. In current review, we aim to investigate treatment outcome of RBV-containing regimens in the treatment of ESRD patients.

Search Strategy and Methods

A Medline search through Pubmed was made using the terms "ribavirin" in combination with "Renal Dialysis", "Kidney Failure, Chronic", "Renal failure" and "hemodialysis" from January 1995 up to August 2008 in the English language. Scopus, Proquest and ISI web of knowledge were also searched with relevant terms. Bibliographies of the articles retrieved were used to find other references.

Inclusion/Exclusion of Studies

Inclusion criteria were as follows: 1) studies that recruited only subjects on hemodialysis or peritoneal dialysis, 2) dose and duration of therapy provided, 3) SVR reported and defined as negative HCV RNA by PCR at least 6 month after end of treatment, 4) inclusion of treatment naïve subjects who had no previous history of IFN based treatment and 5) addition of RBV to IFN or PEG-IFN.

Exclusion criteria were as follows: 1) inclusion of patients with organ transplantation, 2) inclusion of acute HCV infected patients, 3) treatment duration of less than 24 weeks, 4) inclusion of non-dialysis subjects, 6) reporting of viral response rate by methods other than PCR, 7) reporting of only biochemical response rates and 9) inclusion of subjects with acute hepatitis C.

Quantitative Data Synthesis

Studies using similar treatment regimen were pooled together. Results presented were based on intention to treat analysis using raw data extracted from studies. Because of high heterogeneity between studies, we discarded meta-analysis.

Data Extraction

A single investigator (C.E.G.) extracted all relevant data into an electronic database. Occasionally, individual patient data were combined when summary data were not provided. For adverse events, we included any that were reported and did not attempt to attribute causality to underlying comorbidities.

Study Selection

This analysis included prospective studies describing IFN and PEG-IFN based treatment of IFN-naive HD patients with chronic HCV infection documented by means of HCV RNA testing. For the purposes of estimating SVR, we required that studies report HCV RNA results at least 6 months after treatment by using a qualitative or quantitative assay. We excluded the studies that reported only change in transaminase levels or liver histology score as outcome measures because viral eradication is preferable as a measure

of treatment efficacy. Studies that examined acute HCV infection were excluded because of the greater rate of spontaneous HCV RNA clearance in this setting. Studies of PEGIFN that met inclusion criteria were analyzed separately.

Results

We identified 17 relevant studies in our literature review. One study was excluded because it included non-responders to prior therapeutic regimen (33). Another study was excluded because it did not report SVR six month after completion of treatment (34). Another one was excluded because it did not include dialysis patients (35). One study was excluded because it was retrospective (36). One case report and four letters to the editor were also excluded (37-41). One study was excluded because included liver transplant recipient and did not include dialysis patients (42). Another study was excluded because it included relapsers and subjects with normal renal function (43).

Efficacy and safety:

We found studies that enrolled 88 patients, out of whom 59 had SVR, over all SVR rate was 67% (95% CI: 57-76). Because of the significant heterogeneity, routine meta-analysis procedures were not conducted. In one study, twenty HD patients with HCV infection were selected randomly. They received combination therapy with 3 million units (MU) of IFN and 200 mg of RBV three times a week. Six of the nine patients who were treated for 24 weeks (66%) became HCV-PCR-negative by the end of the treatment period. They continued to have sustained virologic response at 6 months after the cessation of therapy. Six of the 11 patients (55%) who were treated for 48 weeks became HCV-PCR-negative at the end, and at 6 months after the cessation of treatment. Of the first six responders, 4 (66%) maintained a sustained virologic response at 1 year post cessation of therapy. Nine of the 11 patients had genotype 4 and 1. No side effects were reported for a RBV dose of 200 mg three times a week (44).

In another study, five patients on hemodialysis with chronic hepatitis C were given interferon-a2b 3 MU thrice weekly for 4 weeks, where after RBV 200–400 mg was added for an intended total treatment period of 28 weeks achieved end of treatment viral response, however, four relapsed 6 months after the treatment cessation (45). RBV plasma concentrations were monitored, using HPLC. Four patients completed the treatment. One patient developed heart failure and died after 14 weeks of treatment but the death was not considered treatment related. Based on plasma concentrations, RBV doses were frequently adjusted initially. The target concentration (10–15 micromol/L) was reached with average daily doses of 170–300 mg RBV. RBV induced anemia was managed with high doses of erythropoietin (20 000–130 000 IU/week). However, this required reduced RBV doses and close monitoring of RBV plasma concentrations and hemoglobin. RBV-induced anemia was managed with high doses of erythropoietin (45) (table1).

Tables 1: Studies using IFN with dose of 3 MU t.i.w plus ribavirin 200-400mg/d

Authors	Subjects in treatment arms (n)	Genotype-1 N (%)	Genotype-4 N (%)	Cirrhosis N (%)	SVR N (%)	Dropout rate N (%)
Mousa et al (44)	20	9	-	0	60%	0
Bruchfeld et al (45)	5	4	1	ND	16%	33%

Tables 2: Studies using PEG-IFN with dose of 135 mcg/w plus 200-400 mg ribavirin every day or every other day

Authors	Subjects in treatment arms (n)	Genotype-1 N (%)	Genotype-4 N (%)	Cirrhosis N (%)	SVR N (%)	Dropout rate N (%)
van Leusen et al (46)	7	5	-	ND	71%	0
Rendina et al (47)	35	ND	-	ND	97%	14%
Bruchfeld et al (48)	6	4	1	ND	50%	16%
Carriero et al (52)	15	12	ND	2	28.6%	71.4%

In another study in seven hemodialysis patients with chronic HCV infection with 135 microg PEG-IFN alfa-2a weekly and 200 mg RBV every other day started. 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. RBV trough plasma levels were monitored regularly by HPLC-technique. All patients completed the treatment. In two patients, the PEG-IFN dose had to be reduced to 90 microg/week because of the adverse events. To achieve the target range (1.5-2.5 microg/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 dose, two to a max of four red cell transfusions were given to four patients. A SVR was reached in five patients (3/5 with genotype 1/4 and 2/2 with genotype 2/3) (46).

In one study thirty-five HD patients with HCV infection received peginterferon alfa-2a 135 microg/week plus RBV 200 mg/day for 24 0r 48 weeks (genotype non-1 and 1, respectively) and dose of RBV was tailored according to plasma concentrations and hemoglobin levels (47). Overall, 34/35 treated patients were HCV RNA negative at week 4 and had undetectable RNA at the end of treatment (47). In six HD patients with HCV infection, using pegylated IFN and RBV 200-400 mg/day was associated with 50% SVR (48). In a prospective and cohort study in 15 HD patients, using pegylated-interferonalpha-2a (135 mcg/week) plus low dose RBV (200 mg/day) was associated with 28.6% SVR and high drop-out (71.4%) and the most frequent side-effect was anemia, which required RBV discontinuation in three patients; while seven (47%) patients received blood transfusions (tabel 2). It indicated that more evidence was requires to make decision regarding the dosage of RBV in HD patients (49).

Discussion

Pegylated interferon plus RBV are standard therapy for patients with chronic HCV infection (50). Treatment in dialysis patients has long been controversial and until recently, the use of RBV was considered to be contra-indicated. Several important points can be identified from our search results. There are just handful non-randomized prospective studies of RBV in chronic hepatitis C individuals on dialysis and the results of these few studies are heterogeneous. However, it appears that addition of RBV to therapeutic regimen can considerably enhance antiviral response. It is also revealed that the target serum concentration of RBV (10-15 micromol/L) can be reached with average daily doses of 170-300 mg and RBV induced anemia can be managed with high doses of erythropoietin (20 000-30 000 IU/week) and low dose of oral iron. Nonetheless, optimal

dose and safety profile of RBV in dialysis patients needs more trials. Until that time, weekly monitoring of CBC and serum RBV concentration and dose adjustment of RBV and erythropoietin is necessary. In conclusion, combination with PEG-IFN alfa-2a (40 kD) with use RBV monitoring drug levels is associated with SVR. However, erythropoietin and transfusion requirements may increase (46, 48, 51).

Studies that investigated PEG-IFN are more recent than those that investigated standard IFN and higher sensitivity of PCR test in these trials can somehow justify this issue. Based on our findings, we suggest administration of RBV with initial dose of 200 mg/d and then weekly dose adjustment based on CBC and serum concentration of RBV.

No study reported viral relapse after attaining SVR. There is high inconsistency of SVR rates. Except one study that reported very low rate of SVR and high rate of dropout (49), it seems that addition of RBV to PEG-IFN in dialysis patients might considerably enhance anti-viral response without heightening adverse events.

Conclusion

According to our findings, individuals on dialysis with chronic hepatitis C who were treated with IFN or PEG-IFN plus RBV can have higher SVR rate than the dialysis patients treated alone with IFN or PEG-IFN. Administration of reduced dose of RBV with close monitoring of CBC and plasma RBV concentration, increase in dose of erythropoietin and in well equipped centers and experts in this field can be safe.

Conflict of interest:

None declared.

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