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Conventional Interferon Alpha Therapy of Chronic Hepatitis C in Patients with End Stage Renal Disease, Six versus Twelve Months? A Meta-Analysis

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Abstract

Background and Aims: Too many small studies have attempted to evaluate the efficacy of standard interferon (IFN) in hemodialysis patients, however, their findings are heterogeneous and absolute guideline for therapy still remains unclear. In current review, we aim to determine which of 24 or 48 week of treatment has greater value in treatment of end stage renal disease in pre-transplantation patients.

Methods: We required that studies report HCV RNA results at least 6 months after treatment cessation. Ninety-five percent confidence intervals (CI) of SVRs were calculated using the approximate normal distribution model. 95% CI of pooled SVR was computed by random effects models. Data manipulation and statistical analyses were undertaken using STATA 8.0.

Results: The pooled SVR for 24 and 48 weeks of standard IFN monotherapy was 38.2% (95% CI=28.9%-47.5%) and 36.9% (95% CI=24.3%-49.4%), respectively. Pooled dropout rate was 24.2% (95% CI=9.5%-38.9%) and 26.9% (95% CI=10.6%-43.3%) in 24 and 48 weeks of IFN monotherapy, respectively.

Conclusions: Standard IFN is still the drug of choice in treatment of HCV in dialysis individuals and 6 months seems to be equal to one-year duration of therapy.

Keywords: Hepatitis C, Hemodialysis, Interferon

Introduction

Hepatitis C virus (HCV) is the major cause of liver disease in industrialized as well as developing countries, that may ultimately lead to liver failure or hepatocellular carcinoma (1, 2).

WHO has estimated that already about 180 million people are infected with HCV, 130 million of these are chronic HCV carriers and at risk of developing liver cirrhosis and cancer. Every year, three to four million individuals are newly infected that 40-60 percent of them will develop chronic hepatitis (3). Although, HCV infection is an emerging disease due to increase in the number of intravenous drug users, however, the prevalence in special group of patients such as those on hemodialysis or with thalassemia is declining (4-9). Patients on chronic hemodialysis (HD) are particularly the major group at the risk of HCV infection. There is a large variety in seroprevalence of HCV in HD

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patients. HCV prevalence in individuals on HD varies geographically, both inter and intra the countries and between the centers in a single city (10).

The reported prevalence of HCV among the HD population varies from 1.9 to 84.6% in different countries and even in various regions in a single country (2, 11-20). Nonetheless, globally, in the last decade, seroprevalence of HCV infection in these kinds of patients has shown a diminishing trend. This reflects the overall of effect of a number of advancements such as broad use of recombinant erythropoietin and resultant decrease need of transfusion, screening of blood products, improvement in the quality and quantity of hemodialysis unit staffs and adherence to the universal precautionary measures (4, 5, 19, 21-29).

The natural history of liver disease in HD patients is complicated due to the Co- morbidities such as cardiovascular diseases. Several studies revealed that the clinical course of chronic HCV infection in these patients was generally asymptomatic and although biochemical dysfunction was often absent in the infected patients, an increased rate of mortality from liver disease had been observed in patients on long-term dialysis (30-35). Nonetheless, in comparison to the chronic hepatitis C patients with normal renal function, chronic hepatitis C infection among HD patients is milder in disease activity. In these patients that are asymptomatic, it is frequently cleared during a long course and is less progressive, perhaps because of immunological abnormalities (36).

Success of antiviral therapy in patients with end stage renal disease (ESRD) has been determined by numerous clinical trials with rates of sustained virological response (SVR) comparable to and even more than the patients with normal renal function that are treated with interferon (IFN) alone. However, virological and biochemical relapse occurs after transplantation due to immunosuppressive medicines and chronic allograft nephropathy and rejection caused by IFN. It has remained a major concern in HCV positive chronic kidney disease patients awaiting renal transplantation and even in those with eradicated viral infection (37-39). Therefore, pre-transplantation treatment and viral eradication has the greatest prognostic value for these patients. At present, Pegylated interferon (PEG-INF) and ribavirin are considered standard treatment in patients with normal renal function. In ESRD patients, ribavirin is not generally prescribed as it is not filtrated through hemodialysis filters, accumulates in serum, and causes dose-related hemolysis (39); however, administration of low dose ribavirin is currently evolving.

Current data are more in favor of IFN than PEG-IFN considering efficacy and safety. Therefore we aimed to investigate two treatment course of conventional interferon monotherapy. We conducted the meta-analysis of available trials to determine whether 48 weeks of treatment is superior to 24 weeks of conventional IFN therapy in ESRD patients prior to kidney transplantation.

Search Strategy and Methods

A Medline search through Pub med was made using the terms “Interferon Alfa-2a” and ”Interferon Alfa-2b” in combination with “Renal Dialysis”, “Kidney Failure, Chronic”, “Renal failure” and “Hemodialysis”. Scopus and ISI web of knowledge were also searched with relevant terms. The information in this report is based on peer reviewed medical articles published from January 1995 up to August 2008 in the English language. Bibliographies of the articles retrieved were used to find other references.

Inclusion/Exclusion of Studies:

To ensure homogeneity among studies, strict inclusion and exclusion criteria were worked out before reviewing the studies and extracting the data. Inclusion criteria were as follows: 1) studies that recruited only subjects on hemodialysis or peritoneal dialysis, 2) dose and duration of therapy reported and 3) SVR reported and defined as negative HCV RNA

Table1. Studies with 24 weeks treatment course of conventional IFN

Authors	Subjects in treatment arms (n)	SVR (95% CI)	Dropout rate (%)
Chan *et al* (56)	11	27% (0.8-53)	ND
Izopet *et al* (57)	12	42% (14-70)	ND
Rostaing *et al* (59)	11	45% (16-74)	ND
Fernandez *et al* (62)	14	14% (0-32)	21%
Campistol *et al* (63)	19	36% (14-58)	52%
Raptopoulou-Gigi *et al* (64)	19	63% (41-85)	31%
Mahmoud *et al* (71)	18	44% (21-67)	11%
Liu *et al* (72)	25	48% (28-68)	0%
Pol *et al* (73)	19	36% (14-58)	5%
Huang *et al* (74)	10	30% (2-58)	40%

by PCR at least 6 month after the end of treatment. In addition, exclusion criteria were as follows: 1) inclusion of patients with organ transplantation, 2) inclusion of acute HCV infected patients, 2) addition of ribavirin to IFN, 3) treatment duration of less than 24 weeks, 4) inclusion of non-dialysis subjects, 5) case reports, small case series and sample size less than ten subjects in treatment arm, 6) reports that contained only biochemical response rates and 8) use of mix dose protocol.

Quantitative Data Synthesis:

Studies using 24 and 48 weeks of treatment duration pooled separately. Results are presented based on objective to do the analysis of the extracted raw data obtained from the studies. Random effects model was used to pool studies together. Q statistic was used to assess heterogeneity among studies and p value >0.1 was considered significant for heterogeneity test. Point estimate of SVR and dropout were calculated as proportions in the form of

Table2. Studies with 48 weeks treatment course of conventional IFN

Authors	Subjects in treatment arms (n)	SVR (95% CI)	Dropout rate (%)
Izopet *et al* (57)	11	64% (36-92)	ND
Hanrotel *et al* (58)	12	33% (6-60)	ND
Ozdemir *et al* (60)	20	40% (19-61)	ND
Buargub *et al* (61)	35	26% (11-41)	34%
Degos *et al* *(65)	37	19% (6-32)	51%
Rocha *et al* (75)	46	22% (10-34)	24%
Huraib *et al* (76)	17	71% (49-93)	5%
Espinosa *et al* (77)	13	38% (12-64)	23%

*- study discontinued because of severe side effects

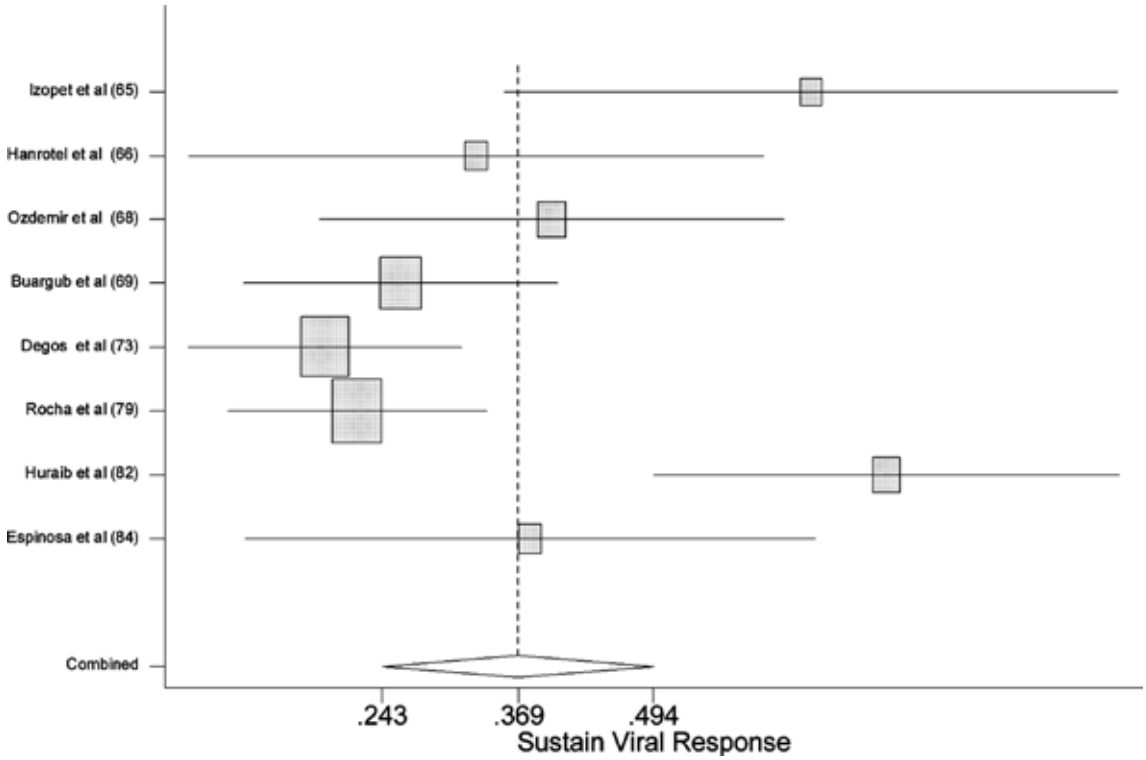

Figure1. Forest plot and pooled SVR rate of studies that have undertaken IFN monotherapy for 1 year

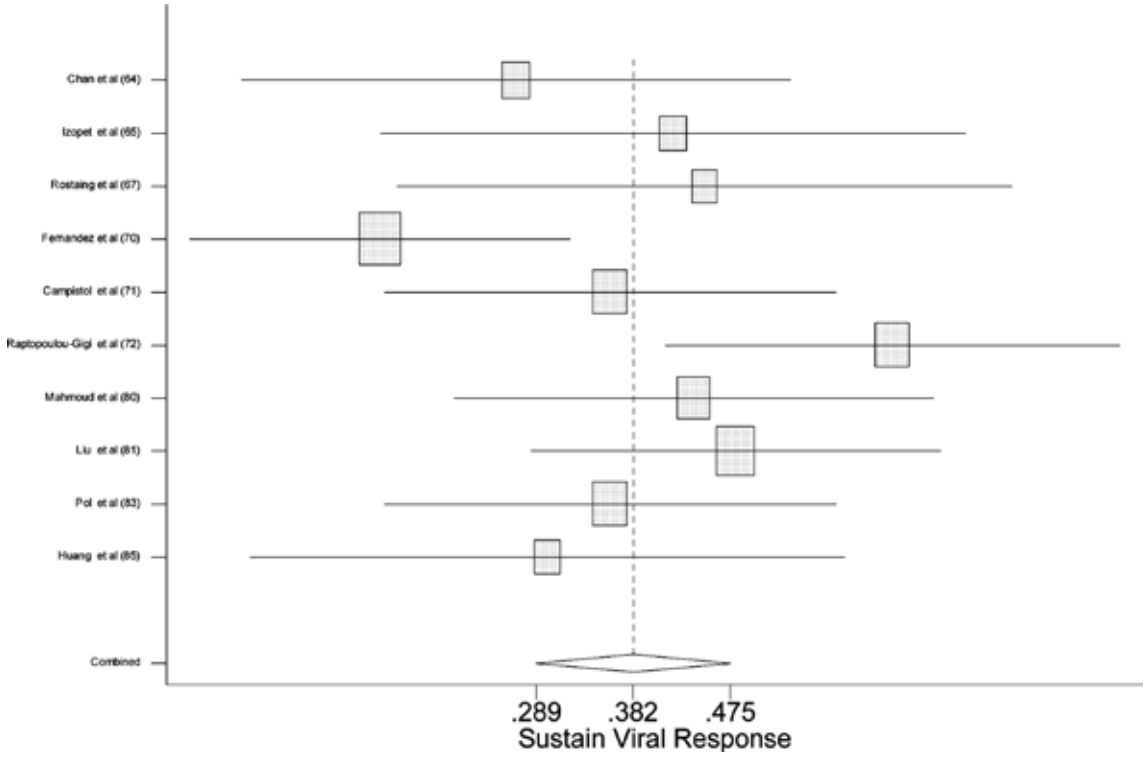

Figure2. Forest plot and pooled SVR rate of studies that have undertaken IFN monotherapy for 6 months.

percentage and their ninety-five percent confidence intervals (CI) were calculated using the approximate normal distribution model. Stata v. 8 software was used to calculate pooled estimates and illustrating graphs.

Data Extraction

A single investigator (C.E.G.) extracted all relevant data into an electronic database. When data were unclear or required assumptions, the other authors were consulted and achieved consensus before recording an entry in the database. In studies that reported HCV RNA results only beyond 6 months after the treatment, it was assumed that as SVR. Occasionally, individual patient data were combined when summary data were not provided. For adverse events, we included any that were reported. Any reported causality was not attributed to underlying comorbidities.

Study Selection:

This analysis included prospective studies describing IFN based treatment of IFN-naive HD patients with chronic HCV infection documented by means of the HCV RNA testing. For the purposes of estimating SVR, we required the studies that reported HCV RNA results at least 6 months after the treatment by using a qualitative or quantitative assay. We excluded studies that reported only change in transaminases levels or liver histology score as outcome measures for the reason that 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. Case reports, letters to the editor, editorials, and small case series were excluded.

Results

We identified 33 relevant studies in our literature review. Five studies were excluded because of low sample size (40-44). In addition, we excluded one study which it included acute hepatitis C patients (45). Three studies were also excluded due to combination therapy with ribavirin (46-48). Moreover, we excluded 4 studies because of using mix doses (49-53). Furthermore, two studies were excluded because of it only reported biochemical response (54) and no state PCR as the method of HCV RNA detection (55). Eighteen studies containing 349 patients met criteria to enter our analysis. Of the eligible studies, ten evaluated 6 months of therapy with IFN.

Qualitative assessment:

The majority of the studies utilized a non-controlled and non-randomized design. There were 12 prospective cohort studies, four control trials and two RCTs. The sequence generation of the randomization process was not mentioned in one of them and no details about allocation concealment and blinding were provided in both. Information regarding withdrawals was described in twelve studies. The criteria for selection of patients and comparability of studies as well as the outcome evaluation were, with few exceptions, satisfactory and homogeneous.

Quantitative analysis:

Seven studies treated patients for a period of forty-eight weeks and one study treated one arm for forty-eight and another for twenty-four weeks. (Table-1 and 2). The pooled SVR was 38.2% (95% CI=28.9%-47.5%) (Figure2) and 36.9% (95% CI=24.3%-49.4%) (Figure1) in 24 and 48 weeks of treatment, respectively. Five studies did not report dropout rate (56-59). Three studies reported SVR after 6 years (60), 18 months (61) and 1 year (62) of follow up. In one study 3 patients had virologic relapse after 16, 17 and 20 months of follow up, respectively (63); and in another study one patient after 14 months of follow up (64). In another RCT study 1 patient became HCV RNA positive one year after cessation of treatment (57). One study was prematurely terminated because of high rate of side effects of IFN (65). Flu like symptoms,

leucopenia and neuropsychiatric symptoms were the most common reasons for IFN withdrawal and the termination of study. There was one reported mortality caused by sudden cardiac death unrelated to IFN (60). Regardless of non-documented intolerances, pooled dropout rate was 24.2% (95% CI=9.5%-38.9%) and 26.9% (95% CI=10.6%-43.3%) at 24 and 48 weeks of monotherapy with IFN, respectively.

Discussion

Several important conclusions can be drawn from the results of this study and analysis. Most studies were found to be non-randomized, prospective and of small sample size. Five studies assessed mix dose of standard IFN with 2 phases of therapy, induction and maintenance; however, none were randomized and did not report any promising results (40, 43, 49-51). From Table 1 and 2 it is clear that all studies suffered inadequate sample size and 95% CI of their sustain viral suppression is so wide that make any estimation and comparison meaningless nonetheless, with entering them to meta-analysis we achieved a narrow pooled estimation of SVR which determined that individuals on dialysis with chronic hepatitis C who treated with IFN alone had higher SVR rate than patients with normal renal function. We already know that SVR of monotherapy with either IFN in normal kidney patients is about 20%, almost half of what we have seen in ESRD patients (66-70). Reduced clearance of IFN leading to its prolonged serum levels and longer half-life has been proposed as a cause of greater antiviral response in this kind of patients. This mechanism is reponsible for higher adverse events and treatment discontinuation in dialysis patients compared to the patients with normal renal function. It was also evident that, one year of IFN monotherapy is quit equal to 6-month therapy regarding efficiency and safety (adverse effects and treatment withdrawal). It is noteworthy that in five patients that received IFN monotherapy, SVR was not durable as anticipated and developed HCV viremia even though they were PCR negative 6 months after completion of therapy.

Conclusions

Almost One-fourth to one-third of dialysis patients with chronic hepatitis C can be successfully treated with conventional IFN monotherapy and 6-months seems to be equal to one-year of therapy.

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