

Pegylated Interferon Alfa 2a and Small Dose Ribavirin in The Treatment of HCV Genotype 4 in End-stage Renal Disease

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Abstract

Background: As hepatitis C virus (HCV) infection is a major health problem in patients with end-stage renal disease (ESRD).

Aim: explore the response rate and adverse effects of pegylated interferon and ribavirin in treating HCV genotype 4 in patients with end stage renal disease (ESRD) waiting renal transplantation.

Patients & Methods: This study included 24 patients with ESRD and active HCV infection as detected by clinical, sonographic, biochemical, serological, virological and histological examination with liver biopsy. All patients were under hemodialysis with HCV antibodies positive > 6 months. Viral genotyping and both qualitative and quantitative PCR were carried out before starting therapy. Treatment was continued for 48 weeks using pegasys 135 µg weekly and ribavirin 200 mg daily. The biochemical and virological responses were evaluated regularly during and after treatment. The sustained virological response (SVR) being evaluated 24 weeks later. The side effects were monitored throughout the treatment period.

Results: Rapid virological response (RVR) after week 4 was achieved in 11/24 (46%) patients. The sustained virological response (SVR) was achieved in 16/24 (66.7%) patients. No break through or relapses were detected during and after treatment respectively. Correlation was found between the viral load before treatment and that at week 4 with $p < 0.001$ and at 12 weeks and between the reduction of hemoglobin and the reduction of viral load at week 12 with $p < 0.045$.

Conclusion: genotype 4 HCV patients with ESRD can be considered for therapy pre-operatively to overcome all the morbidities associated with persistence of HCV after renal transplantation provided that the general condition, the hematological parameters and all other factors of treatment allowed such therapy.

Key words: Pegylated Interferon alfa 2a, Ribavirin, HCV genotype 4, End-stage renal disease.

Introduction:

Despite the introduction of blood-product screening, the increased use of erythropoietin, as well as the adoption of universal precautions and strict infection controls, hepatitis C virus (HCV) infection still remains a major health problem in patients with end-stage renal disease (ESRD)^[1]. The annual incidence of HCV infection in these patients ranges from 0.2% to 6.2%, which is approximately 100–1000 times higher than that in the general population^[2–10]. The reported prevalence rates of chronic HCV infection among ESRD patients ranges from 3.4% to 80% with great geographic variation^[3,8,11–13].

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^[14–16]. ESRD patients with chronic HCV infection

usually have an apparent indolent clinical course with only mildly-elevated serum ALT level^[16–18].

HCV infection is an independent risk factor that increases the risk of death among dialysis patients up to 2.39-fold and increases mortality rates among transplant recipients^[66,67]. Chronic hepatitis C is also associated with mixed essential cryoglobulinaemia^[69], increasing post-transplantation morbidity by enhancing the risk of *de novo* or recurrent HCV-associated glomerulopathies^[70–74]. Recurrence of HCV-associated kidney disease can adversely affect graft survival and has been linked to higher serum creatinine levels^[71–75]. In addition, HCV infection adversely decreases the health-related quality of life in these patients. Although ESRD

patients with chronic hepatitis C receiving renal transplantation (RT) usually have a higher survival rate than those on maintenance dialysis, several studies indicate that these patients have a poorer patient and graft survival after RT^[19-37].

Combination therapy with pegylated IFN and ribavirin has improved the sustained virological response (SVR) rate and is the current standard of care to treat non-uremic patients with chronic hepatitis C^[57,58]. However, ribavirin, which is cleared by the kidneys, may cause severe hemolytic anemia and be dangerous in dialysis patients. Also, only a few studies have assessed the efficacy and safety of pegylated IFN plus low-dose ribavirin to treat ESRD patients with chronic hepatitis C^[59-63]. SVR and treatment-related withdrawal rates after 24 or 48 weeks of combination therapy ranged between 7% and 97%, and 0% and 71%, respectively. These patients needed to receive high-dose erythropoietin (10 000–40 000 IU/week) to maintain adequate dosage for ribavirin during the treatment to achieve excellent on-treatment viral suppression. Furthermore, patients with HCV genotype 2 or 3 infection have higher SVR rates than those with genotype 1 or 4 infection^[62,63].

Similar to ESRD patients who receive conventional IFN monotherapy, a low baseline HCV-RNA level and RVR are positive predictors for SVR in those receiving pegylated IFN monotherapy.^[56]

Thus it is well documented now that in patients with ESRD, chronic hepatitis C virus (HCV) infection leads to enhanced morbidity and mortality, either before^[77,78] or after^[79,80] renal transplantation for end stage renal disease. This increased mortality is related to excessive liver-related death when compared to patients without HCV infection.^[77,81] Moreover, patients undergoing renal transplantation may have an increased risk of HCV-mediated allograft nephropathy and diabetes mellitus. Therefore, viral eradication may improve the outcome of HCV patients after renal transplantation.^[82-85]

The aim of this study is to explore the response rate and adverse effects of pegylated interferon and ribavirin treating HCV genotype 4 in patients with ESRD waiting renal transplantation in Egyptian patients.

Materials and Methods:

This study was conducted in Hepatogastroenterology department and Nephrology department at Theodor Bilharz Research Institute, Giza, Egypt. It includes 24 patients with ESRD and active HCV infection as detected by clinical, sonographic, biochemical, serological, virological and histological examination with liver biopsy. All patients are under hemodialysis as a kidney replacement therapy.

Inclusion Criteria:

1. Age between 18 and 60 years old.
2. Creatinine clearance (Ccr) < 10 ml/min/1.73 m².
3. Receiving regular hemodialysis.
4. Anti-HCV (Abbott HCV EIA 2.0, Abbott Diagnostic, Chicago, IL) positive > 6 months.
5. Detectable serum HCV-RNA (CobasAmplicor HCV Monitor v2.0, Roche MolecularSystems, Pleasanton, CA).

Exclusion Criteria:

1. Neutropenia (neutrophil count, <1,500/mm³).
2. Thrombocytopenia (platelet <90,000/ mm³).
3. Hemoglobin levels < 12 gm/dl.
4. Co-infection with HBV or HIV.
5. Chronic alcohol abuse or evidence of drug abuse.
6. Decompensated liver disease (Child classification B or C).
7. Neoplastic disease.
8. An organ transplant.
9. Immunosuppressive therapy.
10. Poorly controlled autoimmune diseases, pulmonary diseases, cardiac diseases, psychiatric diseases, neurological diseases.
11. Unwilling to have contraception.

Viral genotyping and both qualitative and quantitative PCR were carried out before starting therapy. Treatment was continued for 48 weeks using pegasys 135 µg weekly and ribavirin 200 mg daily unless blood platelets, WBCs or hemoglobin levels were reduced necessitating reduction of the doses of these drugs or the use of erythropoietin to keep hemoglobin level above 10 grams/dl, platelets above 75000/mm³ and WBCs above 1500/mm³.

The biochemical and virological responses were evaluated regularly during and after treatment. The sustained virological response (SVR) being evaluated 24 weeks later. The side effects were monitored throughout the treatment period.

RESULTS:

This study included 24 patients 15 males and 9 females. Age ranges between 22-58years with the mean of 44.75 ± 10.03 . All patients selected fulfilled the inclusion and exclusion criteria. Five patients (4 females and 1 male) were on erythropoietin therapy before enrollment in study. During study, additional 6 patients required use of erythropoietin also. Reduction of interferon doses was commenced in 5 patients to 90 $\mu\text{g}/\text{week}$ because of leukopenia (3 patients) or thrombocytopenia (2 patients) and of ribavirin in additional 4 patients to 800 mg/week. All patients continued treatment during the whole study protocol. Rapid virological response (RVR) after week 4 was achieved in 11/24 (46%) patients. Additional 4 patients showed complete early virological response after week 12 to reach a total

response at week 12 of 15/24 (63%). In addition 2 patients showed slow virological response with 2 log reduction of viral load at week 12. Treatment stopped in the remaining 7 patients. At week 24, one of the 2 patients with slow response showed disappearance of HCV RNA and the other one was still positive for RNA in whom treatment stopped. Thus, at week 24, 16/24 (66.7%) patients showed disappearance of RNA in whom treatment continued till 48 weeks. No break through or relapses were detected during and after treatment respectively. Thus the sustained virological response (SVR) was achieved in 16/24 (66.7%) patients. The biochemical, virological and hematological effects during and after treatment are illustrated in tables 1-5.

Table 1: Patient Characteristics at base line data

Characteristics	Mean \pm SE
Age (n=24)	44.75 \pm 10.03
Male	15 (62.5%)
Female	9 (37.5%)
ALT [IU/l]	66.71 \pm 16.3
AST [IU/l]	64.5 \pm 9.43
Bilirubin mg/dl	1.67 \pm 0.42
HB gm/dl	13.19 \pm 0.68
WBC	50.27 \pm 13.23
Platelet count [$\times 10^9/l$]	185.63 \pm 37.35
PCR IU/ml	1700541.67 \pm 1318399.68

Table 2: Biochemical Findings Before and After Treatment

	Before treatment	After 4 weeks	After 12 Weeks	After 24 weeks	After 48 weeks
ALT [IU/l]	66.71±16.36	57.58±24.47	47.67 ±20.458**	36.13±25.75**	26.63±4.26**
AST [IU/l]	64.5±9.43	54.29±19.01*	46.38±17.47**	43.79±25.97**	36.69±4.21**
Bilirubin mg/dl	1.67±0.42	1.89±0.53 ^a	1.95±0.40 ^a	1.844±0.35 ^a	1.81±0.30 ^a
HB gm/dl	13.19±0.68	12.15±0.54**	11.83±0.55**	11.95±0.40**	11.87±0.60**
WBC	50.27±13.23	41.95±11.27*	47.98±13.76	43.33±11.69	50.24±11.88
Platelet count [× 109/l]	185.63±37.35	157.83±41.48**	147.38±33.38**	222.63±26.23	167.38±35.04**

Data were expressed as mean ± SE

*p<0.05 significant decrease than before treatment

**p<0.01 significant decrease than before treatment

^ap<0.01 significant increase than before treatment

Table 3: PCR Findings Before and After Treatment

	before treatment	After 4 weeks	After 12 weeks	After 24 Weeks	After 48 weeks
PCR IU/ml	1700541.67 ±1318399.68	369772.92** ±934951.50	46705.42** ±15197.88	4852.08** ±1370.85	0

Data were expressed as mean ± SE

**p<0.01 significant decrease than before treatment

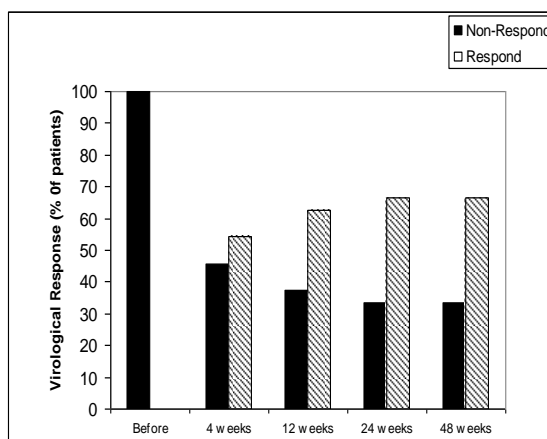


Fig. (1). A virological response during treatment after end of treatment

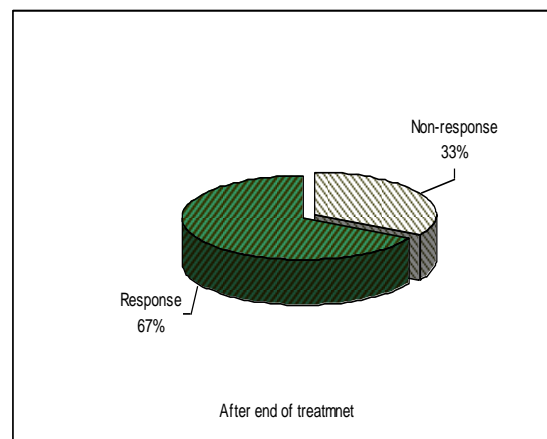


Fig. (2). Sustained virological response (SVR)

Table 4: Biochemical findings 24 weeks after end of treatment

	Before treatment	24 weeks after end of treatment
ALT [IU/l]	66.71±16.36	27.13±0.99**
AST [IU/l]	64.5±9.43	34.56±0.92**
Bilirubin mg/dl	1.67±0.42	2.02±0.07 ^a
HB gm/dl	13.19±0.68	11.71±0.09**
WBC	50.27±13.23	4500.37±326.23**
Platelet count [× 10 ⁹ /l]	185.63±37.35	161.94±10.51**
PCR	1700541.67±1318399.68	0

Data were expressed as mean ± SE

** $p < 0.01$ significant statistical decrease than before treatment

^a $p < 0.01$ significant increase than before treatment

Table 5: correlations between all parameters

	PCR IU/ml before treatment	PCR IU/ml after 12 weeks	HB after 24 weeks
PCR IU/ml before treatment	-----	$r = 0.662^{**}$ $p < 0.01$	-----
PCR IU/ml 4 weeks after treatment	$r = 0.639^{**}$ $p < 0.01$	$r = 0.970^{**}$ $p < 0.01$	-----
HB After 12 weeks	-----	-----	$r = 0.412^*$ $p < 0.05$

** Correlation was found significant between the viral load before treatment and that at 4 weeks (RVR) and 12 weeks (AVR).

* Correlation was found significant between hemoglobin level and reduction of viral load at 12 weeks

Discussion

Combination therapy with pegylated interferon (Peg-IFN) and ribavirin is the standard therapy for chronic HCV infection. In renal transplant recipients, this regimen is usually contraindicated because of an increased risk of graft rejection^[86,87]. In haemodialysed patients, only markedly reduced doses of ribavirin may be used.^[87] However, the exact dose of ribavirin remains unknown and there is a high risk of drug-related toxicity, mainly haemolytic anaemia, due to the increase in ribavirin exposure.^{[88-}

⁸⁹⁾The treatment of ESRD patients with chronic hepatitis C by pegylated IFN monotherapy at a dose of 135–180 µg/week or 0.5–1.1 µg/kg/week for 24–48 weeks resulted in SVR rates of 0–79%, and treatment-related withdrawal rates of 0–56%.^[38-52]. Three meta-analysis studies showed that the SVR and treatment-related withdrawal rates in patients receiving pegylated IFN were 31–37% and 23–28%, which are comparable to conventional IFN^[53,54,55]. Although patients treated with either conventional or pegylated IFN have similar efficacy and safety on the basis of

meta-analysis studies, one head-to-head, randomized trial showed that the overall efficacy and safety in patients treated with pegylated IFN were superior to those treated with conventional IFN^[56].

The dose of peginterferon alpha-2a used in this study was based on the previous data showing that clearance of peginterferon alpha-2a for ESRD patients was about 30-40% lower than that in healthy subjects. A similarly pharmacokinetic profile of peginterferon alpha-2a is observed with 135 µg weekly in dialysis patients compared with 180µg weekly in patients with normal renal function^[56].

Also the dose of ribavirin was selected according the previous studies and pharmacodynamics of the drug in such patients followed by strict monitoring of hemoglobin level during treatment^[59-63].

The sustained virological response (SVR) was achieved in this study in 16/24 (66.7%) patients which is considered similar or even at the higher side of response rates in previous studies in same or other genotypes. Thus, combination therapy with pegylated IFN and ribavirin has improved the SVR rate and is the current standard of care to treat non-uremic or uremic patients with chronic hepatitis C^[57,58].

Anemia was detected in 10 patients in whom reduction of ribavirin dose was done in 4 patients and additional 6 patients required use of erythropoietin to control this side effect. As only few studies have assessed the efficacy and safety of pegylated IFN plus low-dose ribavirin to treat ESRD patients with chronic hepatitis C^[59-63], this study confirm the relative safety and efficacy of this low doses of ribavirin in this population. Also reduction of interferon doses was commenced in 5 patients to 90 µg/week because of leukopenia (3 patients) or thrombocytopenia (2 patients).

No drop- out in this group of population as they are selected properly and encouraged to continue treatment hoping for future safer renal transplant. Also usual side effects were managed in the usual way as in other HCV patients. Fourteen clinical trials have been

identified (269 unique patients); two were controlled studies. The mean overall estimate for sustained virological response (SVR) and drop-out rate in that studies were 37% [95% confidence interval (CI) 28-48] and 17% (95% CI 10-28), respectively. The most frequent side-effects requiring interruption of treatment were flu-like symptoms (17%), neurological (21%) and gastrointestinal (18%). The overall weighted estimate for SVR in patients with hepatitis C virus genotype 1 was 30.6% (95% CI 20.9-48)⁽⁷⁶⁾. Rapid virological response (RVR) after week 4 was achieved in 11/24 (46%) patients which is also comparable to other studies in non- uremic patients and other genotypes. Additional 4 patients showed complete early virological response after week 12 to reach a total response at week 12 of 15/24 (63%). In addition 2 patients showed slow virological response with 2 log reduction of viral load at week 12. At week 24, one of the 2 patients with slow response showed disappearance of HCV RNA. Thus, at week 24, 16/24 (66.7%) patients showed disappearance of RNA.

The low pre-treatment viral load and reduction of hemoglobin level after 12 weeks of treatment were the only factors that correlated with the response to treatment whether at week 4 (RVR) or week 12 (EVR).

Conclusion:

It is concluded from this study that response and tolerability were detected to drug doses used comparable to non-uremic patients with genotype 4 HCV. Thus, genotype 4 HCV patients with ESRD can be considered for therapy pre-operatively to overcome all the morbidities associated with persistence of HCV after renal transplantation provided that the general condition, the hematological parameters and all other factors of treatment allowed such therapy.

It is recommended to carry similar studies in higher number of patients to realize such findings.

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