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Comparing The Efficacy and Safety of (Ombitasvir/ Paritaprevir/ Ritonavir) in Management of Chronic HCV Patients Among Haemodialysis Patients and Those with Normal Renal Functions

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ABSTRACT

Background: In the past, interferon use made it challenging to treat hepatitis C virus (HCV) infection in people with chronic renal disease (IFN). Due to decreased renal clearance of IFN, it was linked to IFN-related adverse events with a significant risk.

Objective: This study aimed to evaluate the antiviral efficacy, safety, and tolerability of ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) in chronic kidney disease patients infected with chronic HCV.

Patients and Methods: This study was conducted on HCV patients who undergo haemodialysis and patients with normal renal functions who had taken OBV/PTV/r. The study was done at the period from May 2017 to May 2018. The study included 47 patients with chronic HCV infection on regular dialysis (study group) and 50 patients with chronic HCV infection (control group).

Results: In our cohort, the mean age of the study group was 43.43 ± 10.56 years while mean age of the control group was 46.80 ± 6.86 years. The majority of the studied groups were males. It was noticed that all enrolled subjects enrolled in the study achieved sustained virological response (SVR) at 12 weeks and 24 weeks. The most frequent adverse effects were fatigue, myalgia and epigastric pain.

Conclusion: Paritaprevir/ritonavir and ombitasvir for 12 weeks were considered to be safe and effective in the treatment of chronic HCV infected patients with end stage renal disease.

Keywords: End-stage renal disease, Hepatitis C virus, Renal impairment, Sustained virological response.

INTRODUCTION

Hepatitis C virus (HCV) is a prominent cause of liver damage among individuals with chronic renal failure and end-stage renal disease (ESRD) receiving frequent haemodialysis (HD), leading to morbidity and mortality [(1)].

It is challenging to treat hepatitis C virus (HCV) infection in ESRD patients. In the past, adding ribavirin to pegylated-interferon (peg-IFN) might be used as a treatment, but it had poor tolerability and efficacy [(2)].

The virus's non-structural proteins are the primary target of recent direct antiviral drugs (DAAs), which also hinder the virus's ability to replicate. These medications successfully elicit a long-lasting virologic response [(3)]. When combined with ribavirin, Qurevo (Ombitasvir + Paritaprevir + Ritonavir) can be used to treat chronic genotype 4 hepatitis C virus infection [(4)].

Egyptian patients with chronic HCV genotype 4 infection who received ombitasvir/paritaprevir/ritonavir (Qurevo) plus ribavirin for 12 or 24 weeks experienced high sustained virological response rates at 12 weeks post-treatment. Patients with chronic HCV genotype 4 infection without cirrhosis or with compensated cirrhosis often tolerated ombitasvir/paritaprevir/ ritonavir (Qurevo) well [(5)].

AIMS OF THE STUDY

The current study aims to assess the percentage of complete recovery or clearance of the virus between HCV patients on HD versus HCV patients with normal renal functions. Also, to assess sustained viral response (SVR) in HCV patients on HD versus HCV patients with normal renal functions.

PATIENTS AND METHODS

Study setting and design:

A cross sectional study was conducted at Outpatient Clinics of Internal Medicine Department of Assiut University Hospital. This study was performed between May 2017 and May 2018.

Ethical consideration:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Assiut University. Written informed consent was taken from all participants. The study was conducted according to the Declaration of Helsinki.

Study participants

This study was carried out on 97 patients with chronic HCV infection divided into 2 groups:

- Group (I): 47 HCV patients on Haemodialysis.
- Group (II): 50 HCV patients with normal renal functions.

Inclusion criteria:

1- Patients with chronic HCV infection.
2- Age from 18-60 years old.
3- Compensated liver cirrhosis.
4- Treatment-naïve patients.

Exclusion criteria:

1- Decompensated liver cirrhosis.
2- Co-infection HCV positive in hepatitis B virus infection.
3- Prior anti-viral therapy.

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Methodology:

1. Baseline evaluation included full history, clinical examination and abdominal ultrasonography to assess compensated or decompensated liver cirrhosis and presence of ascites.
2. Drug regimen:

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3. Follow up of these patients was done by complete blood picture, liver function and HCV-RNA PCR (baseline, at 12th and 24th after end of therapy).

Statistical Analysis

Data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data was expressed in form of mean ± SD or median (range) while nominal data was expressed in form of frequency (percentage). Chi²-test was used to compare the nominal data of both groups in the study while student t-test was used to compare mean of both groups while pre- and post-therapy liver enzymes and hemoglobin level in each group were compared by Paired t test. P value was considered significant if < 0.05.

RESULTS

Demographic Data of Studied Groups (table 1):

Mean age of those patients with ESRD was 43.43 ± 10.56 years while mean age of the control group was 46.80 ± 6.86 years. Majority of studied groups were males (74.4% of ESRD group and 76% of control group).

It was noticed that 21.2% of patients with ESRD and 30% of the control group were smokers. Also, majority of both groups came from rural areas. Age, sex, smoking and residence had no significant differences between both groups (P> 0.05).

Table (1): Demographic data of studied group

Variables	ESRD group (n= 47)	Control group (n= 50)	P value
Age (years)	43.43 ± 10.56	46.80 ± 6.86	0.06
Sex			0.23
Male	35 (74.4%)	38 (76%)	
Female	12 (25.6%)	12 (24%)	
Smoking	10 (21.2%)	15 (30%)	0.34
Residence			0.56
Rural	38 (79.9%)	40 (80%)	
Urban	9 (19.1%)	10 (20%)	

Data was expressed in form of mean (standard deviation), frequency (percentage). P value was significant if < 0.05.

Laboratory Data in Studied Groups (table 2):

Complete Blood Picture:

Hemoglobin level at different times was significantly higher in control group. Baseline hemoglobin, platelets and leucocytes had no significant differences in comparison with data at 3rd month and end of therapy in each of studied groups.

Aspartate Transaminase and Alanine Transaminase:

Aspartate transaminase (AST) and alanine transaminase (ALT) at different times had no significant differences between both groups. Baseline ALT and AST had no significant differences in comparison with data at 3rd month and end of therapy in each of studied groups.

Coagulation Profile:

Coagulation profile at different times had no significant differences between both groups. Baseline coagulation profile had no significant difference in comparison with data at 3rd month and 24 week in each of studied groups.

Table (2): Laboratory data in the studied groups

Variables	ESRD group (n= 47)	Control group (n= 50)	P1 value
Hemoglobin (g/dl)			
Baseline	9.77 ± 1.61	12.29 ± 0.89	< **0.001**
At 3rd month	8.70 ± 0.88	12.81 ± 0.72	< **0.001**
At 24 week	9.13 ± 0.81	13.08 ± 0.50	< **0.001**
P2 value	**0.44**	**0.56**	
TLC (x 10^9/l)			
Baseline	6.41 ± 1.44	6.19 ± 1.51	0.47
At 3rd month	6.31 ± 1.07	6.53 ± 0.98	0.37
At 24 week	7.15 ± 1.50	7.35 ± 1.07	0.45
P2 value	**0.09**	**0.44**	
Platelets (x 10^9/l)			
Baseline	249.3 ± 52.5	269.80 ± 68.9	0.10
At 3rd month	332 ± 42.4	334.5 ± 51.77	0.29
At 24week	350.6 ± 25.45	361 ± 57.20	0.05
P2 value	**0.45**	**0.06**	
AST (U/l)			
Baseline	34.82 ± 8.21	30.48 ± 7.41	0.08
At 3rd month	36.92 ± 6.24	36.26 ± 6.88	0.68
At 24 week	41.07 ± 7.98	40.16 ± 7.27	0.61
P2 value	**0.40**	**0.12**	
ALT (U/l)			
Baseline	40.38 ± 9.70	37.74 ± 9.41	0.36
At 3rd month	39.15 ± 8.50	40.61 ± 8.76	0.48
At 24 week	43.88 ± 9.55	45.41 ± 5.78	0.38
P2 value	**0.19**	**0.48**	
PT (second)			
Baseline	10.34 ± 1.04	11.11 ± 0.98	0.04
At 3rd month	11.01 ± 0.99	12.01 ± 0.99	0.22
At 24 week	10.67 ± 1.10	10.34 ± 1.22	0.60
P2 value	**0.56**	**0.10**	
PC (%)			
Baseline	97.34 ± 6.8	93.74 ± 5.45	0.06
At 3rd month	95.27 ± 2.23	96.40 ± 2.70	0.08
At 24 week	99.35 ± 0.80	97.87 ± 3.35	0.21
P2 value	**0.12**	**0.56**	
INR			
Baseline	1.01 ± 0.02	1.02 ± 0.01	0.37
At 3rd month	0.99 ± 0.03	1 ± 0.02	0.21
At 24 week	1.03 ± 0.01	1.01 ± 0.02	0.32
P2 value	**0.67**	**0.40**	

Data was expressed in form of mean (standard deviation). P value was significant if < 0.05 (P1 compared between both groups while P2 compared between data of the same group). **ESRD**, end stage renal disease; **TLC**, total leucocytic count; **AST**, aspartate transaminase; **ALT**, alanine transaminase; **PT**, prothrombin time; **PC**, prothrombin concentration; **INR**, international randomized ratio.

Kidney Function among the studied groups (table 3):

Kidney function at different times were significantly higher in the ESRD group but kidney function at the same group had no significant between baseline data in comparison to data at 3rd month and at the end of therapy. Also, albumin/creatinine ratio (ACR) was significantly higher at ESRD group at baseline and at the end of therapy in comparison to control group. It was noticed that none of the control group developed proteinuria at end of therapy.

Table (3): Kidney function in studied groups

Variables	ESRD group (n= 47)	Control group (n= 50)	P1 value
Urea (mg/dl)			
Baseline	156.46 ± 39.10	28.32 ± 4.08	**< 0.001**
At 3rd month	152.34 ± 29.79	29.67 ± 5.31	**< 0.001**
At 24 week	162.46 ± 24.19	36.62 ± 5.83	**< 0.001**
P2 value	**0.26**	**0.22**	
Creatinine (mg/dl)			
Baseline	9.33 ± 1.45	0.72 ± 0.17	**< 0.001**
At 3rd month	8.15 ± 1.81	0.76 ± 0.19	**< 0.001**
At 24 week	8.58 ± 1.22	0.80 ± 0.21	**< 0.001**
P2 value	**0.09**	**0.78**	
ACR			
Baseline	289.56 ± 55.87	20.56 ± 4.45	**< 0.001**
At 24 week	299.01 ± 60.11	19.56 ± 3.33	**< 0.001**
P2 value	**0.44**	**0.40**	

Data was expressed in form of mean (standard deviation). P value was significant if < 0.05 (P1 compared between both groups while P2 compared between data of the same group). **ESRD**, end stage renal disease; **ACR**, Albumin creatinine ratio

Sustained virological response (SVR) and adverse effects in both studied groups (table 4, figure 1):

It was noticed that all enrolled subjects enrolled in the study achieved SVR at 12 weeks and 24 weeks. Adverse effects of therapy in the current are summarized at Table 8. The most frequent adverse effects were fatigue (94% of ESRD vs. 70.2% of control group; P<0.001), myalgia (37% of ESRD vs. 60% of control group; P= 0.02) and epigastric pain (60% of ESRD vs 70% of control group). It was noticed that frequency of nasopharyngitis was significantly in the control group (42.6% of ESRD vs. 72% of control group; P< 0.001) but irritability was significantly higher in the ESRD group (34% of ESRD vs. 2% of control group; P< 0.001).

Table (4): SVR and adverse effects in both Studied groups

Variables	ESRD group (n= 47)	Control group (n= 50)	P1 value
SVR at 12 weeks	47 (97%)	50 (97%)	---
SVR at 24 weeks	47 (97%)	50 (97%)	---
Irritability	16 (34%)	1 (2%)	**< 0.001**
Nasopharyngitis	20 (42.6%)	36 (72%)	**< 0.001**
Purities	22 (46.8%)	19 (38%)	0.41
Insomnia	4 (8.5%)	14 (28%)	**0.01**
Fatigue	47 (94%)	33 (70.2%)	**< 0.001**
Myalgia	37 (74%)	25 (53.2%)	**0.02**
Epigastric pain and Nausea	60 %	70%	**0.01**

Data was expressed in form of mean (standard deviation), frequency (percentage). P value was significant if < 0.05. **ESRD**, end stage renal disease; **SVR,** sustained virological response.

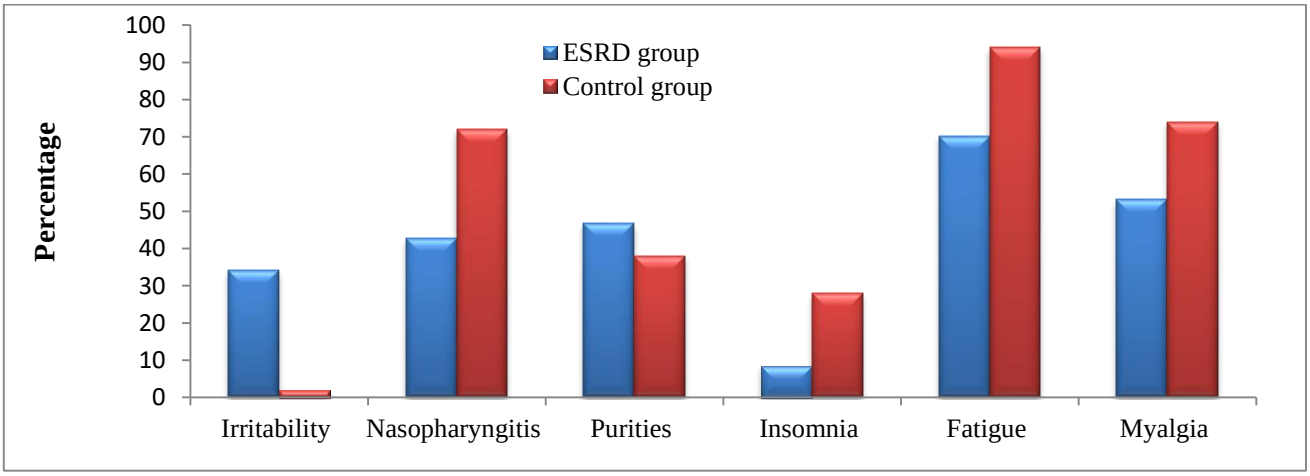

Figure (1): Adverse effects of therapy in the current study group during course of therapy.

DISCUSSION

Our cohort, the mean age of those patients with ESRD was 43.43 ± 10.56 years while mean age of the control group was 46.80 ± 6.86 years. The majority of the studied groups were males (74.4% of ESRD group and 76% of control group).

Farahat and colleagues [6] conducted a cross-sectional study on people who were enrolled in the outpatient clinics of the Family Health Center of "Kafr Tanbedy" and the Internal Medicine Department of the Faculty of Medicine, Menoufia University, Egypt. Their results were in agreement with ours. Patients with CKD had an average age of 45.55±8.565 years.

Similarly, the 2014 Egyptian Demographic Health Survey (EDHS) and the 2015 Egyptian Health Issues Survey (EHIS) both revealed greater rates of chronic HCV infection in Egyptian males, which can be ascribed to males having a higher burden of schistosomiasis disease [7].

Mohamoud and colleagues [8] discovered a greater frequency of chronic HCV infection in males and rural residents than in females and urban dwellers in their systematic review and meta-analysis.

In contrast to our findings, **Ghonemy and colleagues** [9] found that Egyptian patients with CKD were significantly older. The authors conducted a cross-sectional study to examine the epidemiology and risk factors for CKD in 15 dialysis centres at governmental hospitals in El Sharkia, Egypt. One thousand four patients were chosen, with 62.2% males and 37.8% females. The patients' average age was 52.03 + 14.67 years.

Patients with CKD commonly encounter anaemia as a side effect. The issue manifests early in kidney disease, gets worse as kidney function deteriorates, and is associated with unfavourable disease outcomes [10].

Patients with ESRD had considerably lower haemoglobin levels than the control group in the current investigation. **New and colleagues** [11] examined the prevalence of anaemia, by stage of CKD, in the general diabetic population, which is consistent with our findings. Gradually worsening CKD was associated with an increase in anaemic prevalence. The majority of anaemic patients had CKD stage 3 (by number of patients).

New and colleagues [11] examined the prevalence of anaemia, by stage of CKD, in the general diabetic population, which is consistent with our findings. With deteriorating CKD, anaemia became more common with time. The majority of anaemia cases were found in CKD stage 3 patients.

In terms of the primary outcomes of the present study, we found that all enrolled subjects achieved SVR at 12 weeks and 24 weeks, with no significant difference between ESRD patients and the control group.

Lawitz and colleagues [12] conducted two phase 3, open-label, multicenter studies in patients with stage 4 or 5 CKD to evaluate the effectiveness of OBV/PTV/r for HCV-infected patients, which is consistent with our findings. SVR12 rate was 95% overall (63/66); 1 patient experienced virologic failure.

OBV/PTV/r without DSV produced SVR rates of 90.5–98.1% and shown great tolerance in a phase III research from Japan [13]. A case series of 10 patients with genotypes 1a, 1b, and 4 infections was used to assess the efficacy of the OBV/PTV/r regimen in hemodialysis patients with cirrhosis. SVR12 has a 100% success rate with few adverse effects [14].

In the present study, the serum AST and ALT did not change significantly at the end of therapy in both studied groups. These findings can be attributed to the fact that both serum AST and ALT levels were within the normal range in the majority of the patients.

Generally, OBV/PTV/r in patients with HCV is safe with few incidences of serious adverse events. In the present study, The most frequent adverse effects were fatigue (94% of ESRD vs. 70.2% of control group; P<0.001), and myalgia (74% of ESRD vs. 53.2% of control group; P= 0.02). It was noticed that the frequency of nasopharyngitis was significantly in the control group (42.6% of ESRD vs. 72% of control group; P< 0.001) but irritability was significantly higher in the ESRD group (34% of ESRD vs. 2% of control group; P< 0.001).

Lawitz and colleagues [12] reported that 37% (27/37) of patients taking ribavirin experienced adverse events that necessitated a dose change, which is consistent with our findings. Only one patient, though, had to stop taking their medication.

STUDY LIMITATIONS

The main stuyd limiations included relatively samll sample size and short term durtaion of follow up.

CONCLUSION

The use of paritaprevir/ritonavir and ombitasvir (75/50/12.5mg) daily plus ribavirin for 12 weeks was safe and effective in the treatment of chronic HCV genotype 4 infected patients with end stage renal disease on regular haemodialysis.

RECOMMENDATION

Further studies are recommended to use OBV/PTV/r therapy in CKD patients with larger sample size to exclude its side effects, also using Qurevo in diabetic and hypertensive patients.

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Author contribution: Authors contributed equally in the study.

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