

Comparison between the effect of Two Regimens for Hepatitis C Treatment (Querevo and Ribavirin) and (Sofosbuvir, Daclatsvir and Ribavirin) on Patients above and below the Age of 60 Years

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ABSTRACT

Background: the goal of antiviral treatment is to prevent complications of the disease, mainly cirrhosis and HCC. New therapy options, known as direct acting antiviral (DAA) regimens, offer the promise of increased success rates complimented by shorter treatment durations, improve side effect profiles, and simplified treatment monitoring.

Aim of the Work: to compare between the effect of oral antiviral treatment especially (Querevo and Ribavirin) and (Sofosbuvir, Daclatasvir and Ribavirin) between elderly patients above 60 years and young people below this age as regard: Response to treatment, Development of complication.

Patients and Methods: the study was conducted on 100 Egyptian patients they were divided into 2 groups each one received one of the two treatment regimens then each group divided into 2 subgroups, subgroup A include patients below 60 years and subgroup B include patients above 60 years. The selected patients were subjected to History taking, Complete physical examination, Pelviabdominal ultrasound, Laboratory investigations: complete blood count, bilirubin and liver enzymes before and after treatment, INR, creatinine, albumin, HBs Ag, HIV antibodies and Alpha feto proteins, HCV RNA.

Results: there is no significant difference between two treatment regimens. Both regimens show cure rate about 94%, 96% achieved SVR with (sofosbuvir daclatasvir and ribavirin regimen), (querevo and ribavirin regimen) respectively. Both regimens are effective in elderly patients above 60 years as young patients below this age in both regimens, response of treatment in both regimens in elderly patients above 60 years is 96%. Gender doesn't affect treatment outcome. Anemia develop in 34% of patients receiving sofosbuvir, daclatasvir and ribavirin regimen, and in 58% of patients receiving querevo and ribavirin regimen. Females developed anemia more frequent than males in both regimens. Both regimens developed hepatobiliary complication, 12%, 18% developed hyperbilirubinemia with (sofosbuvir daclatasvir and ribavirin regimen), (querevo and ribavirin regimen) respectively.

Conclusion: treatment with (sofosbuvir daclatasvir and ribavirin regimen) or (querevo and ribavirin regimen) is highly effective with little differences between them; also age and gender have no role in achieving SVR. Complications such as anemia and hyperbilirubinemia occur in treatment with both regimens and more frequent with (querevo and ribavirin regimen).

Keywords: Sofosbuvir, Daclatasvir, Querevo, Ribavirin, SVR

INTRODUCTION

Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and HCC. Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15-30% within 20 years ⁽¹⁾. The risk of HCC in persons with cirrhosis is approximately 2-4% per year ⁽²⁾. Elderly patients with chronic HCV infection have been an understudied population due to several factors. These factors include exclusion of subject older than 65 years of age in several clinical trials, reluctance to treat HCV infection in elderly due to fear of dealing with more HCV therapy related adverse effects, co morbidities and risk factors of aging such as decreased glomerular filtration rate that may cause more severe hemolytic anemia with ribavirin and interactions of interferon and ribavirin with several potential geriatric drugs ⁽³⁾. Paritaprevir, a protease inhibitor boosted with ritonavir, and ombitasvir, an NS5A inhibitor, are effective for the

treatment of persons infected with genotype 4 HCV ⁽⁴⁾. Sofosbuvir has shown a good safety profile in clinical trials; an overall improved tolerability was seen with sofosbuvir compared to interferon based regimens ⁽⁵⁾.

AIM OF THE WORK

To compare between the effect of oral antiviral treatment especially (Querevo and Ribavirin) and (Sofosbuvir, Daclatasvir and Ribavirin) between elderly patients above 60 years and young people below this age as regard: Response to treatment, Development of complication.

PATIENTS AND METHODS

This is a case control study that was conducted on 100 Egyptian patients, 50 patients received (Sofosbuvir, Daclatasvir and Ribavirin) and other 50 patients received (Querevo and

Ribavirin). Patients were recruited in the virology unit, Ahmed Maher Teaching Hospital and Ain Shams University. With following Inclusion criteria: Hepatitis C Ab positive patients, Patients 18 years or older, HCV RNA >15 at initial screening, and exclusion criteria: Patients with decompensated liver cirrhosis (Child Pugh B or C), Patients with hepatocellular carcinoma, Coinfected patient with HBV or HIV. Patients were assigned into: Group (A): include 50 patients below 60 years subdivided into two subgroups each subgroup received one of the two treatment regimens. Group (B): include 50 patients above 60 years subdivided into two subgroups each subgroup received one of the two treatment regimens. Patients approval was taken through informed consent then all patients were subjected to: History taking, Complete physical examination search for signs of decompensation, Pelviabdominal ultrasound: identified focal lesions cirrhosis, splenomegaly and pelvic collections, Laboratory investigations: complete blood count, bilirubin and liver enzymes before and after treatment, INR, creatinine, albumin, HBs Ag, HIV antibodies and Alpha feto proteins, HCV RNA in serum or plasma by a sensitive qualitative and quantitative molecular method. **Ethical considerations: The study was approved by the Ethics Board of Ain Shams University and an informed written consent was taken from each participant in the study.**

Statistical analysis: Collected information were coded, tabulated, and analyzed using IBM spss statistics (Statistical Package for Social Sciences) software version 22.0, IBM corp., Chicago, USA, 2013. Statistically descriptive information were done for quantitative information as minimum & maximum of range and mean ± SD (standard deviation). Inferential analysis was done for quantitative variables using independent T-test in cases of two independent groups with normally distributed data. Inferential analyses in qualitative information, for independent variables were done using Chi square test for differences between proportions. The level of significance was estimated by p-value < 0.050 is significant, otherwise is non-significant.

RESULTS

Table (1): Compares response of treatment between two regimens: shows that both regimens are effective with p value <0.05 with no different in treatment with either regimen

PCR		Groups		T-Test	
		Sofosbuvir Daclatasvir and Ribavirin	Quervo and Ribavirin	t	P-value
Before	Mean	2701059.340±	3666460.880±	-0.613	0.541
	±SD	5361347.688	9762455.022		
After	Mean	28559.240±	190419.920±	-0.888	0.373
	±SD	129799.959	1282093.125		
Differences	Mean	2672500.100±	3476040.960±		
	±SD	5370315.807	9904851.781		
Paired Test	P-value	0.001*	0.017*		

Table (2): Compares response of treatment with sofosbuvir, daclatasvir and ribavirin regimen between patients below and above 60 years: shows no differences as regarding age

PCR Sofosbuvir Daclatasvir and Ribavirin		Subgroups		T-Test	
		Group A	Group B	t	P-value
Before	Mean	2078234.840±	3323883.840	-	0.417
	±SD	2090515.163	±7314872.969		
After	Mean	50136.560±	6981.920	1.180	0.244
	±SD	179484.402	±34834.600		
Differences	Mean	2028098.280±	3316901.920		
	±SD	2119487.832	±7316072.853		
Paired Test	P-value	<0.001*	0.033*		

Table (3): Compares response of treatment with quervo and ribavirin regimen between patients below and above 60 years: shows no differences as regarding age

PCR Quervo and Ribavirin		Subgroups		T-Test	
		Group A	Group B	T	P-value
Before	Mean	2651942.360±	4680979.400±	-	0.468
	±SD	2837224.103	13578954.778		
After	Mean	362558.320±	18281.520±	0.948	0.348
	±SD	1812716.600	91332.600		
Differences	Mean	2289384.040±	4662697.880±		
	±SD	3616694.385	13575190.515		
Paired Test	P-value	0.004*	0.099		

Table (4): Compares the effect of gender on outcome of HCV treatment with both regimens: shows that gender has no role on effectiveness of HCV treatment

Groups	PCR	Gender		T-Test	
		Male	Female	T	P-value
		Mean±SD	Mean±SD		
Sofosbuvir Daclatasvir and Ribavirin	Before	2478374.682±3274101.546	2876025.857±6614786.257	-0.258	0.798
	After	29158.545±104591.178	28088.357±148550.243	0.029	0.977
Quervo and Ribavirin	Before	5374092.905±14865421.269	2429899.759±2273891.535	1.054	0.297
	After	431614.190±1977835.960	15762.000±84800.190	1.135	0.262

Table (5): Compares the development of anemia with both regimens: shows significant increase of anemia with both regimens and increased incidence with quervo and ribavirin regimen

Hb		Groups		T-Test	
		Sofosbuvir Daclatasvir and Ribavirin	Quervo and Ribavirin	T	P-value
Before	Mean ±SD	13.424±1.913	13.080±1.701	0.950	0.344
After	Mean ±SD	12.140±1.520	11.380±1.517	2.503	0.014*
Differences	Mean ±SD	1.284±1.431	1.700±1.677		
Paired Test	P-value	<0.001*	<0.001*		

Table (6): Compares the development of anemia with sofosbuvir, daclatasvir and ribavirin regimen in patients above and below 60 years: shows no significant difference

Hb Sofosbuvir Daclatasvir and Ribavirin		Subgroups		T-Test	
		Group A	Group B	T	P-value
Before	Mean ±SD	13.596±1.661	13.252±2.156	0.632	0.530
After	Mean ±SD	12.436±1.489	11.844±1.522	1.390	0.171
Differences	Mean ±SD	1.160±1.416	1.408±1.464		
Paired Test	P-value	<0.001*	<0.001*		

Table (7): Compares the development of anemia with quervo and ribavirin regimen in patients above and below 60 years: shows no significant difference

Hb Quervo and Ribavirin		Subgroups		T-Test	
		Group A	Group B	T	P-value
Before	Mean ±SD	13.396±1.632	12.764±1.742	1.324	0.192
After	Mean ±SD	11.644±1.427	11.116±1.587	1.237	0.222
Differences	Mean ±SD	1.752±1.702	1.648±1.684		
Paired Test	P-value	<0.001*	<0.001*		

Table (8): Compares the development of hyper-bilirubinemia with both regimens: shows significant increase of hyper-bilirubinemia with quervo and ribavirin regimen

TBI		Groups		T-Test	
		Sofosbuvir Daclatasvir and Ribavirin	Quervo and Ribavirin	T	P-value
Before	Mean ±SD	1.009±0.510	0.792±0.222	2.768	0.007*
After	Mean ±SD	0.923±0.443	0.930±0.486	0.077	0.938
Differences	Mean ±SD	0.087±0.513	-0.138±0.460		
Paired Test	P-value	0.238	0.039*		

Table (9): Compares the effect of gender on development of complication with treatment with both regimens: shows that development of anemia more common with female in both regimens

Groups		Gender		T-Test	
		Male	Female	T	P-value
		Mean±SD	Mean±SD		
Sofosbuvir Daclatasvir and Ribavirin	Hb Before	14.295±1.766	12.739±1.764	3.095	0.003*
	Hb After	12.764±1.345	11.650±1.489	2.737	0.009*
	TBI Before	0.973±0.402	1.038±0.587	-0.441	0.661
	TBI After	0.915±0.318	0.929±0.527	-0.109	0.914
Quervo and Ribavirin	Hb Before	13.767±1.557	12.583±1.649	2.564	0.014*
	Hb After	11.871±1.556	11.024±1.409	2.009	0.050*
	TBI Before	0.848±0.236	0.751±0.206	1.539	0.130
	TBI After	1.057±0.582	0.838±0.387	1.601	0.116

DISCUSSION

This study was applied on 100 patients divided into two groups each group received one of both treatment regimen then each group subdivided into two sub groups, subgroup A containing 25 patients below 60 years and subgroup B containing 25 patients above 60 years. The study include 43 males and 57 females, 21 of males and 29 of

females received quervo and ribavirin regimen, while 22 of males and 28 of females received sofosbuvir, daclatasvir and ribavirin regimen. This study shows that both regimens achieved high efficacy with p value of both <0.05 and no significant differences between them p value 0.377. Gender and age don't affect outcome of treatment with p value (0.977 with sofosbuvir, daclatasvir and ribavirin regimen, 0.262 with quervo and ribavirin regimen as regarding gender) and (0.244 with sofosbuvir, daclatasvir and ribavirin regimen, 0.348 with quervo and ribavirin regimen as regarding age) and this is in agreement with *Abdel-Moneim et al.*⁽⁶⁾, and *Ahmed et al.*⁽⁷⁾, that reported Sofosbuvir plus daclatasvir, with or without ribavirin achieved high efficacy and safety in HCV genotype 4 patients. Their effect were accompanied with attenuation of liver fibrosis. Patients treated with sofosbuvir, daclatasvir and ribavirin regimen shows efficacy 94 % and this matched with *Omar et al.*⁽⁸⁾ study, that including >18,000 Egyptian patients with HCV infection, about 95% achieved SVR 12. It was concluded that sofosbuvir plus daclatasvir with or without ribavirin regimen is safe and effective for the treatment of Egyptian patients with chronic hepatitis C genotype 4. Also in agreement with *Pol et al.*⁽⁹⁾ study that documented the combination of sofosbuvir and daclatasvir with or without ribavirin had high antiviral potency, with >90% SVR rate in patients with chronic HCV infection. This study agrees with *Fontaine et al.*⁽¹⁰⁾ study that concluded the combination of sofosbuvir and daclatasvir was associated with a high rate of SVR in treatment of genotype 4 HCV. SVR was 86%-100%, according to patients' baseline characteristics and therapeutic regimen. Patients treated with Quervo and ribavirin regimen shows efficacy 96 % and this matched with *Crespo et al.*⁽¹¹⁾ study that reported high SVR rates of 96.2% were reported in HCV GT4 infected patients treated with OBV/PTV/r (n=122) with or without RBV. This study shows little differences with *David and Nina*⁽¹²⁾ study that examined the efficacy of a 12-week course of ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in adults with chronic HCV genotype 4 infection; For the 86 treatment-naïve recipients of ombitasvir plus paritaprevir plus ritonavir without ribavirin, an SVR12 was achieved in 91% (40 of 44) compared with an SVR12 rate of 100% (42 of 42) in participants treated with ombitasvir plus paritaprevir plus ritonavir with

ribavirin. The study, showed an excellent treatment response with a 24-week regimen of ombitasvir plus paritaprevir plus ritonavir for genotype 4 infection, particularly if ribavirin is added to the regimen. *Gretja et al.*⁽¹³⁾ study reported that SVR12 rate of 100% were observed among GT4- infected treatment naïve and treatment experienced patients receiving ombitasvir plus paritaprevir with RBV. In the current study with sofosbuvir, daclatasvir and ribavirin regimen (24/25) of patients above 60 years achieved SVR12, while (23/25) of patients below 60 years achieved SVR 12 and with quervo and ribavirin regimen (24/25) of patients above 60 years achieved SVR12 and the same with patients below 60 years. So age doesn't affect treatment outcome and this is in agreement with *Conti et al.*⁽¹⁴⁾ study that demonstrated age per se does not influence the success of IFN- free treatments in elderly patients with CHC and that all DAA regimens seem well tolerated and safe, also in subjects with advanced liver disease and in those aged 75 years or older. Also *Ossama et al.*⁽¹⁵⁾ study shows that neither age nor any of the pretreatment biochemical markers including hemoglobin, leukocytic count, platelet count, ALT, AST, albumin, INR, bilirubin, and PCR for HCV RNA showed significant correlation with treatment outcome. (27/28) of females treated with sofosbuvir, daclatasvir and ribavirin regimen achieved SVR12, the female that doesn't achieve SVR, is below 60 years. (28/29) of female treated with quervo and ribavirin regimen achieved SVR12, the female that doesn't respond is above 60 years. So gender does not affect treatment outcome and this is similar to *Paola et al.*⁽¹⁶⁾ study that did not identify meaningful association between virological responses and gender. In this study (17/50) 34% of patients receiving sofosbuvir, daclatasvir and ribavirin regimen developed anemia with p value <0.001 , (10/25) of them above age of 60 and (11/28) of them were females. There is increased incidence of anemia with females p value before treatment was 0.003 and after treatment was 0.009. Age doesn't increase incidence of anemia p value 0.171. While occurrence of hyperbilirubinemia (6/50) 12% of patients is not significant in this regimen p value 0.238. 29/50) 58% of patients receiving quervo and ribavirin regimen developed anemia with p value <0.001 , (15/25) of them above age of 60 and (16/29) of them were females. There is increased incidence of anemia with females p value before treatment was 0.014 and after treatment was 0.050. Age doesn't

increase incidence of anemia p value 0.222. Occurrence of hyperbilirubinemia (9/50) 18% of patients is significant in this regimen with p value 0.039. In comparison between two regimens there is increased incidence of anemia more with quervo and ribavirin regimen with p value 0.014. In case of comparison of hyperbilirubinemia between two regimens although p value is 0.938 (non-significant) although there is significant increase with quervo and ribavirin regimen it is due to increases bilirubin before treatment with sofosbuvir, daclatasvir and ribavirin regimen with p value before treatment was 0.007. Female gender shows increased incidence of anemia before and after treatment with both regimens. As regarding anemia, this study is mismatched with Poordad *et al.* ⁽¹⁷⁾ study that reported daclatasvir in combination with sofosbuvir and ribavirin developed anemia in (20%) of patients. In **Ahmed *et al.*** ⁽⁷⁾ study, non-cirrhotic naïve patients were treated with sofosbuvir plus daclatasvir for 12 weeks. Ribavirin was added to this regimen when treating cirrhotic patients and/ or treatment experienced patients. The adverse event was anemia in (5.67%) of patients. **Blaise *et al.*** ⁽¹⁸⁾ reported about Safety profile of different SOF combination that the mean change in haemoglobin level associated with regimens that contained RBV versus those that didn't contain RBV was -2.4g/dl versus -0.4g/dl after 12 weeks of therapy, and this is in agreement with this study that shows the mean change in haemoglobin level (1.284 ± 1.431). **Attia *et al.*** ⁽¹⁹⁾ In this retrospective multicenter study adverse events were reported in 5 patients out of 101 who received PTV/OBV/r/RBV regimen, mean age was (61 +/- 5 years old) one had anaemia, one had hyperbilirubinemia and 3 patients had non-specific side effects. SOF / DCV / RBV also showed hepatobiliary complication in 31% of the developed side effects, and were (92/45188, 0.2%) in the treated patients' group. Haematological complications were (96/45188, 0.2%) in treated patients with anaemia being the most common one (76/45188, 0.16%) in treated patients. This study is in agreement with **Hironao *et al.*** ⁽²⁰⁾ and **Menon *et al.*** ⁽²¹⁾ studies that reported during treatment with ombitasvir, paritaprevir, and ritonavir with or without ribavirin, mild to moderate increase in serum bilirubin concentration, has been reported in some cases. **Liu *et al.*** ⁽²²⁾ documented that in patients receiving paritaprevir, 23% had elevation in total bilirubin (>2.25mg/dl), mainly indirect (unconjugated) bilirubin levels, without elevation in liver enzymes.

CONCLUSION

This study shows that treatment with (sofosbuvir daclatasvir and ribavirin regimen) or (quervo and ribavirin regimen) is highly effective with little differences between them, also age and gender have no role in achieving SVR. Patients in this study developed some complications as anemia and hyperbilirubinemia that occur in treatment with both regimens and more frequent with (quervo and ribavirin regimen).

CONFLICTS OF INTEREST

There are no conflicts of interest.

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