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Evaluation of Ledipasvir plus Sofosbuvir for Treatment of Compensated and Decompensated HCV Cirrhotic Patients

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ABSTRACT

Background:unlike human immunodeficiency virus (HIV) and hepatitis B virus (HBV), hepatitis C virus (HCV) infection is a curable disease. Current direct acting antiviral agent (DAA) targets are focused on HCV NS3/4A protein (protease), NS5B protein (polymerase) and NS5A protein. The first generation of DAAs includes boceprevir and telaprevir, which are protease inhibitors and were approved for clinical use in 2011. The cure rate for genotype 1 patients increased from 45% to 70% when boceprevir or telaprevir was added to standard PEG-IFN/ribavirin. More effective and less toxic second generation DAAs supplanted these drugs by 2013. The second generation of DAAs includes sofosbuvir, simeprevir and fixed combination medicines containing ledipasvir plus sofosbuvir and Viekira Pak. These drugs increase cure rates to over 90% without the need for interferon and effectively treat all HCV genotypes. With these drugs the "cure HCV" goal has become a reality. The aim of this study was to assess of ledipasvir plus sofosbuvir as treatment of HCV infection in patients with advanced liver disease including cirrhotic patients with child B and C. Patients and methods:in this prospective study, seventy five HCV PCR positive patients were classified into three groups according to child score. Each group included twenty five patients. All patients received ledipasvir plus sofosbuvir for six months.

For all patients thorough medical history, clinical examination, kidney function tests, liver function tests, complete blood count, pelvi-abdominal ultrasound, HCVantibodies, hepatitis C viral RNA, quantitative, HbsAg, alpha fetoprotein as baseline screening. HCV PCR done for all patients at end of treatment and three months later to detect sustained virological response (SVR12). Patients with combined HCV and HBV infection, hepatic or extrahepatic malignancies and late child C were excluded.

Results: showed that no statistical significant difference were detected in patients of group A as regard liver **function tests** before and after treatment and SVR12 achieved by 96%. Patients of group B showed significant statistical difference as regard liver **function tests** before and after treatment with SVR12 achieved by 88%. In patients of group C there were significant statistical difference in liver **function tests** with SVR12 achieved by 80%. Also there were clinical improvement in patients of group B and C after end of treatment.

Conclusion:it could be concluded that there will be a dramatic improvement in HCV therapy followed the introduction of oral medicines that directly inhibiting the replication cycle of HCV. The combination pill contains a fixed-dose of ledipasvir 90 mg and sofosbuvir 400 mg, two direct-acting antiviral agents against HCV. Ledipasvir is an inhibitor of the NS5A protein, which is required for HCV replication. Sofosbuvir inhibits the HCV NS5B RNA-dependent RNA polymerase, which is also required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form a pharmacologically active triphosphate that can incorporate into the HCV RNA. Ledipasvir plus sofosbuvir can be used safely in treatment of compensated and decompensated post hepatitis C liver cirrhosis. SVR12 can be achieved by 96% in patients with early cirrhosis (child A), 88% in patients with child B cirrhosis and 80% in patients with child C with subsequent improvement in liver functions.

Keywords: -Ledipasvir plus sofosbvir, Advanced liver disease, HCV infection, Direct acting antivirals.

INTRODUCTION

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV). The virus persists in the liver in about 85% of infected patients [(1)]**.** HCV is spread primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment, and transfusions. An estimated 150–200 million people worldwide are infected with hepatitis C. The prevalence of hepatitis C virus (HCV) infection in Egypt is the highest in the world[(2)]**.** The HCV genome contains a single large open reading frame

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encoding for a polyprotein of about 3100 amino acids. From this initially translated polyprotein, the structural HCV protein core (C) and envelope glycoproteins 1 and 2 (E1, E2), p7, and the six non-structural HCV proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B, are processed by both viral and host proteases [3]**.** The spectrum of clinical manifestations of HCV infection varies in acute versus chronic disease. Acute infection with HCV is most often asymptomatic and leads to chronic infection in about 85% of cases [4]**.** Aminotransferases become elevated approximately 6-12 weeks after exposure (range 1-26 weeks). Jaundice as a clinical feature of acute hepatitis C will be present in less than 25% of infected patients. Therefore, acute hepatitis C will not be noticed in most patients [4]**.** Other Symptoms are generally mild and vague flu like symptoms including: decreased appetite, nausea, tenderness in the area of the liver, fever fatigue muscle or joint pains and weight loss[5]**.** Chronic hepatitis C is defined as the presence of detectable viral replication for at least six months. Most experience minimal or no symptoms during the initial few decades of the infection [6]**.**

The most frequent complaint is fatigue. Less common manifestations are nausea, weakness, myalgia, arthralgia, and weight loss. HCV infection has also been associated with cognitive impairment [7]**.** Around 30 to 40% of patients with chronic hepatitis C have an extrahepatic manifestation of HCV[8]**.** Complications of hepatitis C occur almost exclusively in patients who have developed cirrhosis.

Findings that can be associated with cirrhosis are hepatomegaly and/or splenomegaly on physical examination, elevated serum bilirubin concentration, hypoalbuminemia, or low platelets. Other clinical findings associated with chronic liver disease may be found such as spider angioma, caput medusae, palmar erythema, testicular atrophy, or gynecomastia. Most of these findings are found in less than half of cirrhotic patients, and therefore none is sufficient to establish a diagnosis of cirrhosis [9]**.** Direct acting antivirals (DAAs) have changed the landscape of HCV therapy. The combination pill contains a fixed-dose of ledipasvir 90mg and sofosbuvir 400 mg, two direct-acting antiviral agents against HCV. Ledipasvir is an inhibitor of the NS5A protein, which is required for HCV replication. Sofosbuvir inhibits the HCV NS5B RNA-dependent RNA polymerase, which is also required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form a pharmacologically active triphosphate that can incorporate into the HCV RNA [10]**.** The goal of antiviral therapy is to cure hepatitis C via a sustained elimination of the virus. A sustained elimination of HCV is achieved if the HCV RNA remains negative twelve weeks after the end of treatment .Importantly, long-term benefits of SVR are the reduction of HCV-related hepatocellular carcinoma and overall mortality [11]**.** In past decompensated liver disease was contraindication for HCV treatment till **James Bredfeldt *et al*.** assessed treatment with ledipasvir plus sofosbuvir, and ribavirin in patients infected with HCV genotypes 1 or 4 with cirrhosis and moderate or severe hepatic impairment results were very promising but unfortunately few patients were infected with genotype 4 which predominate in Egypt [12]**.**

PATIENTS AND METHODS

This study has been conducted on seventy five patients recruited from Ahmed Maher Teaching Hospital, Sayed Galal Hospital and Al-Hussein Hospital in the period from June 2015 to June 2016. All patients received ledipasvir plus sofosbuvir for six months. For all patients thorough medical history, clinical examination, kidney function tests, liver function tests, complete blood count, pelvi-abdominal ultrasound, HCV antibodies, hepatitis C viral RNA, quantitative, HbsAg, alpha fetoprotein as baseline screening. HCV PCR done for all patients at end of treatment and three months later to detect sustained virological response (SVR12). Patients with combined HCV and HBV infection, hepatic or extrahepatic malignancies and late child C were excluded. Five ml from patient's venous blood were withdrawn on EDTA tubes and sera were separated and kept at -20 Celsius degree .sera were used for viral RNA quantification according **Lohr *et al*.** and for measuring all the biochemical parameters[13]**.** They were divided into three groups according to child score:

Group (A): Included twenty five HCV PCR +ve patients. They were 12 (48%) male patients and 13(52%) female patients, their ages ranged from 35-65 years with mean age 47.920 ± 7.783 years. Child score of these patients was 5 with mean score 5.000 ± 0.001.

Group (B): Included twenty five HCVPCR +ve patients. They were 12 (48%) male patients and 13(52%) female patients, their ages ranged from 40-69 years with mean age 52.880±8.584 years. Child score of these patients was 7-9 with mean score 7.560± 0.712.

Group (C): Included twenty five HCV PCR+ve patients. They were 12 (48%) male patients and 13(52%) female patients, their ages ranged from 52-75 years with mean age 61.080±6.271 years .Child score of these patients was 10-12 with mean score 10.600 ± 0.816.

Statistical measures

Some statistical measures as mean, standard deviation (SD), t student test, correlation coefficient (r) of two variables, Chi-square test (X2) and Probability (P) were used.

RESULTS:

This study showed that ledipasvir plus sofosbuvir can be used safely for treatment of compensated and decompensated post HCV liver cirrhosis. Sustained virological response (SVR12) achieved by 96% in patients with early cirrhosis (child A), 88% in patients with child B cirrhosis and 80% in patients with child C (table 1). There were improvement in liver functions test regarding INR, serum bilirubin level and serum albumin level between patients of group B and C (table 2, 3 and 4 respectively). Clinically there were improvement in degree of ascites in patients of group Band C (table 5).

DISCUSSION

Hepatitis C is a disease with significant global impact. According to the World Health Organization there are 130 - 150 million people chronically infected with the hepatitis C virus (HCV), corresponding to 2-2.5% of the world's total population. There are considerable regional differences. In Egypt, the prevalence is >10% [(14)]**.**

A dramatic improvement in HCV therapy followed the introduction of oral medicines that directly inhibiting the replication cycle of HCV. These medicines, called direct-acting antivirals (DAAs), target three important regions within the HCV genome: NS3/4A protease, NS5A and NS5B RNA-dependent polymerase [(15)]**.**

This study enrolled 25 patients (group A) with Child–Pugh score 5 (Child A) sustained virological response at week 12 after end of treatment (SVR12) was achieved by 96%. There were 25 patients (group B) with early decompensated post HCV cirrhosis Child B SVR12 achieved by 88% and 25 patients (group C) with advanced liver disease Child C classification SVR12 was achieved by 80% . These results came in close correlation with results of James **Bredfeldt *et al*.** where they assessed treatment with ledipasvir plus sofosbuvir, and ribavirin in patients infected with HCV genotypes 1 or 4. Cohort A enrolled patients with cirrhosis and moderate or severe hepatic impairment who had not undergone liver transplantation. Cohort B enrolled patients who had undergone liver transplantation those without cirrhosis; those with cirrhosis and mild, moderate, or severe hepatic impairment. Patients were assigned randomly (1:1) to receive 12 or 24 weeks of a fixed-dose combination tablet containing ledipasvir and sofosbuvir, once daily, plus ribavirin. The primary end point was sustained virologic response at 12 weeks after the end of treatment (SVR12).

They enrolled 337 patients, 332 (99%) with HCV genotype 1 infection and 5 (1%) with HCV genotype 4 infection. In cohort A (nontransplant), SVR12 was achieved by 86%–89% of patients. In cohort B (transplant recipients), SVR12 was achieved by 96%–98% of patients without cirrhosis or with compensated cirrhosis, by 85%−88% of patients with moderate hepatic impairment, by 60%–75% of patients with severe hepatic impairment. Response rates in the 12- and 24-week groups were similar. There were few data about efficacy of ledipasvir plus sofosbuvir treatment in patients with genotype 4 HCV infection beside there were no effective and safe treatments for chronic hepatitis C virus infection of patients who have advanced liver disease[(12)]**.**

There were improvement from baseline to posttreatment liver functions (ALT, AST, s. albumin, total bilirubin, INR, degree of ascites and recurrence of hepatic encephalopathy if it occurred previously) in patients with Child B and C, these results comes in close correlation with that of **JamesBredfeldt *et al.*** where there were change from baseline to post-treatment week 4 in MELD scores in patients with Child–Pugh B and C disease. The scores were calculated using the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time [(12)]**.**

Manns *et al*. found that Ledipasvir-sofosbuvir and ribavirin provided high rates of SVR12 for patients

with advanced liver disease, including those with decompensated cirrhosis where they did an open-label study at 34 sites in Europe, Canada, Australia, and New Zealand. Cohort A included patients with Child-Turcotte-Pugh class B (CTP-B) or CTP-C cirrhosis who had not undergone liver transplantation. Cohort B included post-transplantation patients who had either no cirrhosis; CTP-A, CTP-B, or CTP-C cirrhosis.In cohort A, among patients with genotype 1 HCV, SVR12 was achieved by 20 (87%) of 23 CTP-B patients with 12 weeks of treatment; 22 (96%) of 23 CTP-B patients with 24 weeks of treatment; 17 (85%) of 20 CTP-C patients (12 weeks treatment); and 18 (78%) of 23 CTP-C patients (24 weeks treatment) [(16)].

In cohort B, among patients with genotype 1 HCV, SVR12 was achieved by 42 (93%) of 45 patients without cirrhosis (12 weeks treatment); 44 (100%) of 44 patients without cirrhosis (24 weeks treatment); 30 (100%) of 30 CTP-A patients (12 weeks treatment); 27 (96%) of 28 CTP-A patients (24 weeks treatment); 19 (95%) of 20 CTP-B patients (12 weeks treatment); 20 (100%) of 20 CTP-B patients (24 weeks treatment); one (50%, 3-98) of two CTP-C patients (12 weeks treatment); and four (80%) of five CTP-C patients (24 weeks treatment). These results comes in close correlation with current study with slight differences due to duration of treatment, number of patients, HCV genotype and addition of ribavirin.

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Table (1): Comparison between three groups regarding real time PCR in patient's three groups before (**T1)**, at the end of treatment (**T2)**, and three months after the end of treatment (**T3)**.

PCR		Groups								Chi-Square	
		Group A		Group B		Group C		Total			
		N	%	N	%	N	%	N	%	X^2	P-value
T1	Negative	0	0.00	0	0.00	0	0.00	0	0.00	x	x
	Positive	25	100.00	25	100.00	25	100.00	75	100.00		
T2	Negative	25	100.00	25	100.00	25	100.00	75	100.00	x	x
	Positive	0	0.00	0	0.00	0	0.00	0	0.00		
T3	Negative	24	96.00	22	88.00	20	80.00	66	88.00	3.030	0.220
	Positive	1	4.00	3	12.00	5	20.00	9	12.00		
Chi-Square	T1-T2	<0.001*		<0.001*		<0.001*					
	T1-T3	<0.001*		<0.001*		<0.001*					
	T2-T3	0.100		0.234		0.059					

Table (2): Comparison between INR values of three groups before (**T1)**, at the end of treatment (**T2)**, and three months after the end of treatment (**T3)**.

INR		Groups			ANOVA		TUKEY'S Test		
		Group A	Group B	Group C	F	P-value	A&B	A&C	B&C
T1	Range	1.0 - 1.0	1.25 - 1.8	1.68 - 2.1	450.889	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ±SD	1.000 ± 0.001	1.468 ± 0.138	1.846 ± 0.105					
T2	Range	1.0 - 1.0	1.22 - 1.55	1.45 - 2.0	243.313	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ±SD	1.000 ± 0.001	1.363 ± 0.077	1.609 ± 0.151					
T3	Range	1.0 - 1.0	1.22 - 1.7	1.45 - 2.0	202.190	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ±SD	1.000 ± 0.001	1.375 ± 0.103	1.641 ± 0.167					
Paired Samples Test	T1-T2	1.000	<0.001*	<0.001*					
	T1-T3	1.000	0.001*	<0.001*					
	T2-T3	1.000	0.327	0.088					

Table (3): Comparison between total bilirubin serum levels of three groups before (**T1)**, at the end of treatment (**T2)**, and three months after the end of treatment (**T3)**.

TB		Groups			ANOVA		TUKEY'S Test		
		Group A	Group B	Group C	F	P-value	A&B	A&C	B&C
T1	Range	0.4 - 1.2	1.6 - 3.2	2.45 - 3.5	323.345	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ±SD	0.744 ± 0.212	2.228 ± 0.367	2.921 ± 0.328					
T2	Range	0.4 - 1.1	1.2 - 2	1.45 - 3	95.617	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ±SD	0.684 ± 0.193	1.488 ± 0.172	2.025 ± 0.539					
T3	Range	0.4 - 1	1.2 - 2.7	1.45 - 3.8	52.783	<0.001*	<0.001*	<0.001*	0.002*
	Mean ±SD	0.664 ± 0.173	1.654 ± 0.484	2.197 ± 0.771					
Paired Samples Test	T1-T2	0.040*	<0.001*	<0.001*					
	T1-T3	0.032*	<0.001*	<0.001*					
	T2-T3	0.327	0.044*	0.065					

Table (4): Comparison between serum albumin levels of three groups before (**T1)**, at the end of treatment (**T2)**, and three months after the end of treatment (**T3)**.

S. Albumin		**Groups**			**ANOVA**		**TUKEY'S Test**		
		Group A	**Group B**	**Group C**	**F**	**P-value**	**A&B**	**A&C**	**B&C**
T1	**Range**	3.8 - 4.6	2.7 - 3.3	2.4 - 2.8	502.450	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ±SD	4.132 ± 0.234	3.032 ± 0.149	2.637 ± 0.112					
T2	**Range**	4 - 5	3 - 3.6	2.2 - 2.9	454.921	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ±SD	4.340 ± 0.242	3.268 ± 0.157	2.782 ± 0.147					
T3	**Range**	3.8 - 5	2.4 - 3.6	2.2 - 2.9	252.728	<0.001*	<0.001*	<0.001*	<0.001*
	Mean ±SD	4.332 ± 0.256	3.164 ± 0.308	2.730 ± 0.208					
Paired Samples Test	**T1-T2**	<0.001*	<0.001*	<0.001*					
	T1-T3	<0.001*	0.020*	0.016*					
	T2-T3	0.327	0.045*	0.045*					

Table (5): Comparison between presence of ascites in patients of three groups before (**T1)**, at the end of treatment (**T2)**, and three months after the end of treatment (**T3)**.

Ascites1		**Groups**								**Chi-Square**	
		Group A		**Group B**		**Group C**		**Total**			
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**X^2**	**P-value**
T1	**No**	25	100.00	10	40.00	1	4.00	36	48.00	47.115	<0.001*
	Mild	0	0.00	15	60.00	24	96.00	39	52.00		
T2	**No**	25	100.00	24	96.00	19	76.00	68	90.67	9.769	0.008*
	Mild	0	0.00	1	4.00	6	24.00	7	9.33		
T3	**No**	25	100.00	22	88.00	17	68.00	64	85.33	10.460	0.033*
	Mild	0	0.00	1	4.00	3	12.00	4	5.33		
	Moderate	0	0.00	2	8.00	5	20.00	7	9.33		
Chi-Squa	**T1-T2**	1.000		<0.001*		<0.001*					
	T1-T3	1.000		<0.001*		<0.001*					
	T2-T3	1.000		0.352		0.047*					