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Safety & Efficacy of Direct Acting Antiviral (Sofosbuvir & Daclatasvir) in Treatment of Chronic HCV in HIV-HCV Co-Infected Egyptian Patients

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Abstract

HCV therapy has been transformed by the discovery of direct-acting antiviral medicines, which have led to better cure rates, shorter treatment durations, and greater tolerability. To assess the effectiveness and safety of DAAs in treating chronic HCV in patients with HIV and co-infection with chronic HCV infection exclusively, we conducted this research. 50 individuals with nave HCV infection who were also HIV-infected were studied at Abbasia Fever Hospital compared to 50 patients with HCV mono infection who were monitored for six months. In the course of a 12-week therapy with a combination of daclatasvir 90 mg and sofosbuvir 400mg+/- ribavirin 800mg daily, serial assessments of safety parameters, viral and immunological correlates, and adherence were made. CD4 T-lymphocyte count of 200 cells/mL or above was required for patients with HIV/HCV co-infection to be on antiretroviral treatment (ART). Conclusions and findings: HCV-HIV co-infected patients (48/50, 96%) had a strong sustained virological response (SVR) compared to HCV mono-infected patients (49/50, 98%). A substantial drop in the AST and ALT levels was seen at both the end of and 12 weeks following therapy in both groups. Otherwise, the haematological and biochemical values have not changed much. Sofosbuvir/daclatasvir was shown to be safe in patients with HIV/HCV co-infection, with the most prevalent side effects being tiredness (58 percent) and headache (42 percent), and no significant adverse events or drug-drug interactions with ART were recorded.

Keywords: Sofosbuvir, Daclatasvir, Chronic HCV, HIV-HCV, Co-Infected**.**

1. Introduction

About 130–170 million individuals worldwide were infected with the virus, and it was discovered in 10–30 percent of all HIV-infected persons [1].

Cirrhosis and hepatocellular cancer are more common in HIV/HCV co-infected individuals than in people infected with HCV alone [2].

However, antiretroviral treatment has lowered the influence of HIV co-infection on the course of HCV illness, but not abolished it. HIV/HCV-infected patients, on the other hand, are more likely to die from liver-related causes. Priority should be given to preventing and treating HCV infection in those with HIV and HCV co-infection [2].

Patients who achieve sustained virological response (SVR), which is defined as undetectable HCV RNA in their blood 12 weeks after the conclusion of HCV therapy, have a lower risk of liver-related morbidity and death, such as HCC or liver transplantation. A decrease in the frequency of HCV-related comorbidities may thus have a significant long-term economic impact. SVR patients had greater post-treatment employment rates than those who fail therapy [3]. This extends to their job productivity.

PegIFN-free oral regimens of direct-acting antivirals (DAAs) increased the effectiveness and tolerance of HCV therapy in coinfection. HCV NS5A NS5B inhibitors Daclatasvir (DCV) and Sofosbuvir (SOF) both have minimal anti-retrovirals medication interactions, which are generally managed by simple dosage modifications for DCV [5]. [6]

Tolerability was excellent in HIV/HCV co-infected patients treated with a broad variety of combination antiretroviral therapy regimens (cART) for 12 weeks, with high rates of long-term viral suppression (SVR).

Sofosbuvir and Daclatasvir were tested for their safety and effectiveness in the treatment of patients with both HCV and HIV.

2. Methods

At the Abbasia Fever Hospital, one of the National AIDS Program's treatment facilities, this retrospective cohort research was conducted on 50 HCV-HIV co-infected patients and 50 HCV mono-infected patients. The National AIDS Program and Benha University's Gastroenterology and Hepatology Department authorised the research.

HIV infection confirmed by western blot test; confirmed HBs antigen negative; alpha-fetoprotein within 3* normal range of laboratory; effective contraception (Women of childbearing potential should use an effective contraception; Male patients and their female partners must also practise eective contraception) both during treatment and for the 3-months post-therapy; no breast-feeding; signed informed consent and w w w.

Excluded patients include the following. Co-morbid conditions such as severe hypertension, heart failure, significant coronary heart disease, COPD, major uncontrolled depressive illness and solid transplant organs (renal, heart or lung) that are contraindicated to DAAs: pregnancy or unwillingness to comply with adequate contraception; breastfeeding; anaemia 10 g/dL; thrombocytopenia; eGFR 30; and eGFR 30.

According to the Abbasia Fever hospital protocol and Egyptian national guidelines for antiretroviral therapy, December 2017: efavirenz 600 mg one tablet

daily + truvada (tenofovir 300 mg + emtricitabine 200 mg) one tablet daily and a direct acting anti-viral drug regimen according to NCCVH Guidelines for the Management of Adult Patients with HCV Infection divided into two groups: Sofosbuvir 400mg+Daclatasvir 90mg for 12 weeks is a simple treatment option. This combination of Sofosbuvir 400 mg + Daclatasvir 90 mg + Ribavirin 600 mg for 12 weeks is not simple to administer.

History-taking with emphasis on signs of liver cell failure (lower limb edoema, hematemesis/melena, ascites, hepatic encephalopathy) was performed on all patients prior to therapy. Special attention to indications of Liver Cell Failure throughout the examination HCV RNA PCR quantitation by quantitative HCV sAg and HBcAb total. Pelvi-abdominal ultrasonography, HIV RNA PCR., CD4 count.

At weeks 4 and 12, clinically (new symptoms or signs) encountered by the included patients after commencing treatment will be examined and documented in pre-prepared sheets. This will help establish the patient's safety during therapy. Tests for liver function include the bilirubin, serum albumin, and INR (internal natriuretic peptide), as well as ALT and AST (alanine and aspartate) (AFP).

After end of treatment: -Evaluation of efficacy of treatment by follow up HCV RNA by PCR will be done at week 12 & 24.

Follow up of HIV disease will be done every 6 months by: HIV RNA by PCR., CD4 count after treatment.

2.1Statistical analysis

Data were analyzed using SPSS software, version 22.0 (IBM, Armonk, NY, USA) for Windows. Categorical data were presented as number and percentages, Chi square ($\chi 2$) and Fisher's exact tests were used to analyze them. Quantitative data were tested for normality using Shapiro-Wilks test assuming normality at $P>0.05$. Normally distributed variables were expressed as mean ±standard deviation and analyzed by Student "t" test for 2 independent groups, and repeated measures ANOVA for 3 matched variables, while non parametric ones were presented as median and inter-quartile range (IQR), and analyzed by Mann Whitney U test for 2 independent groups or Friedman's test for 3 matched variables within the same group. Significant repeated ANOVA or Friedman's test was followed by post hoc multiple comparisons using Bonferroni adjusted tests to detect the significant pairs. $P \leq 0.05$ was considered significant.

3. Results

The present study included 50 patients HCV-HIV co-infected patient (40 males and 10 females) with mean age (63.9 ± 6.3), and 50 patients HCV mono-infection (33 males and 17 females) with mean age (33.7 ±7.66). All enrolled patients were Child A, all of them completed the study duration without any major problems, quantitative HCV PCR was negative for all patients at the end of treatment, yet 12 weeks after ending treatment 2 patient (4%) had HCV relapse of HIV-HCV co-infection group, and 1 patient (2%) of HCV mono-infection group.

As regard to route of HIV infection, the commonest was through intravenous drug abuse in 64%, different sexual routes in 8%, blood transfusion in 14%, and the rest was not identified.

As regard laboratory data, statistically non-significant change in hemoglobin, TLC, platelet count, serum bilirubin, serum albumin, INR, AFP in two groups otherwise there is significant decrease in AST and ALT during follow-up at 4,8,12 weeks in two groups

Ultra-sonographic findings sow hepatomegaly in 40% of patients of HIV-HCV co-infection group compared to 18% in patients with mono-infection group on follow up along study duration, but had no significant difference in liver parenchyma, portal vein diameter, spleen size, no presence of ascites or hepatic focal lesions.

There Is Significant Increase Of Cd4 Count Before Treatment, At The End Of Treatment And After 12 Weeks Of End Of Treatment

Regarding to side effects in HIV-HCV co-infection group fatigue (74%), headache (48%), insomnia (34%), diarrhea (24%), nausea (22%), and pruritus (14%). Compared to HCV mono-infection group fatigue (42%), headache (36%), insomnia (8%), diarrhea (2%) and no nausea or pruritus. No side effect requiring drug discontinuation or hospitalization.

Table (1) Comparison in CBC findings, over time among two groups.

Hb (gm/dl)	**HCV only group (n=50)**			**HCV-HIV co-infected group (n=50)**			**St."t" test**	**P**
	Mean	**± SD**	**Range**	**Mean**	**± SD**	**Range**		
Before ttt	14.3	1.65	8.2-17.3	13.1	1.62	10.1-16.1	3.98	<0.001 (HS)
4 weeks after ttt	14.1	1.46	10.7-16.3	12.8	1.66	10.2-15.9	4.15	<0.001 (HS)
12 weeks after ttt	13.9	1.53	10.3-16.5	13.1	1.39	11-15.6	2.8	0.006 (S)
P(Repeated measures ANOVA)	0.25 (NS)			<0.001 (HS)				

Significat pairs		------		Hb After 4 Weeks versus Hb Before TTT Hb After 4 Weeks versus Hb After 12				
WBCs Before ttt	6.28	1.55	2.2-9.68	6.93	2.14	0.9-11.8	1.73	0.086 (NS)
WBCs 4 weeks after ttt	6.63	1.18	4.4-8.8	6.21	1.72	1.1-10.2	1.43	0.155 (NS)
WBCs 12 weeks after ttt	6.75	2.22	3.1-13.2	6.58	1.77	1.3-10.9	0.41	0.68 (NS)
P(Repeated measures ANOVA)		0.39 (NS)		0.002 (S)				
Significat pairs		--------		After 4 Weeks versus Before TTT After 4 Weeks versus After 12 Weeks				
PLTs Before ttt	194.0	62.4	94-397	234.0	71.3	84-424	2.98	0.004 (S)
PLTs 4 weeks after ttt	183.2	38.5	104-261	231.9	75.4	83-421	4.07	<0.001 (HS)
PLTs 12 weeks after ttt	180.9	52.8	71-294	246.2	75.8	86-423	4.99	<0.001 (HS)
P(Repeated measures ANOVA)		0.071 (NS)		<0.001 (HS)				
Significat pairs				After 4 Weeks versus Before TTT After 4 Weeks versus After 12 Weeks				

Table (1) shows changes in CBC findings in studied patients before treatment and during treatment at week 4 and week12, which shows statistically non-significant change in hemoglobin, TLC or platelet count over follow-up through 4 weeks and 12 weeks.

Table (2) Comparison in liver function, INR and AFP tests findings over time among two groups.

ALT	**HCV only group (n=50)**			**HCV-HIV co-infected group (n=50)**			**ZMWU test**	**P**
	Median	**IQR**	**Range**	**Median**	**IQR**	**Range**		
Before ttt	33.5	24.5-56.3	7-102	40.0	25-74	10-169	1.27	0.204 (NS)
4 weeks after ttt	31.0	22.8-41	14-85	29.5	19-41.3	15-54	0.83	0.41 (NS)
12 weeks after ttt	30.0	24.8-48	15-109	28.0	18.8-41	14-52	2.13	0.034 (S)
P(Friedman's test)	0.078 (NS)			<0.001 (HS)				
Significat pairs				Before versus 12 w 4W versus 12 w				
AST Before ttt	37.5	26.8-56.3	15-106	39.5	28-66.5	18-213	0.16	0.87 (NS)
AST 4 weeks after ttt	40.0	28.8-49	19-101	30.0	25-40	18-59	2.5	0.012 (S)
AST 12 weeks after ttt	37.5	25.8-68.8	20-148	28.0	22-41	16-52	3.5	<0.001 (HS)
P(Friedman's test)	0.14 (NS)			<0.001 (HS)				
Significat pairs	------			Before versus 4 w Before versus 12 w				
T. bilirubin Before ttt	0.7	0.52-1.1	0.3-1.7	0.85	0.6-1.03	0.26-1.3	1.03	0.30 (NS)
T. bilirubin 4 weeks after ttt	0.9	0.6-1,4	0.3-2.8	0.80	0.68-1.03	0.4-1.6	1.0	0.32 (NS)
T. bilirubin 12 weeks after ttt	0.9	0.7-1.1	0.4-1.8	0.80	0.7-0.9	0.1-1.2	1.92	0.053 (NS)
P(Friedman's test)	0.052 (NS)			0.14 (NS)				
Significat pairs	---------			----------				
AFP Before ttt	6.1	4-9.8	2-22	7.05	3-9.02	0.9-27.9	0.27	0.78 (NS)
AFP 4 weeks after	6.0	5-8	3-18	6.4	3.5-9.3	1.6-15.6	0.52	0.6 (NS)

ttt								
AFP 12 weeks after ttt	6.5	5-12.5	3-35	6.1	4.2-9.5	1.45-16.9	1.52	0.128 (NS)
P(Friedman's test)	0.15 (NS)			0.135 (NS)				
Significat pairs	--------			------				
Serum albumin	Mean	± SD	Range	Mean	± SD	Range	St."t"	P
Before ttt	4.29	0.33	3.5-4.8	4.18	0.39	3.6-5.1	1.49	0.14 (NS)
4 weeks after ttt	4.28	0.32	3-4.9	4.10	0.29	3.5-4.6	2.89	0.005 (S)
12 weeks after ttt	4.38	0.48	2.8-5.33	4.17	0.25	3.7-4.7	2.73	0.007 (S)
P(Repeated measures ANOVA)	0.41 (NS)			0.39 (NS)				
Significat pairs	----------			--------				
INR Before ttt	1.16	0.16	0.91-1.46	1.14	0.11	0.9-1.4	0.89	0.37 (NS)
INR 4 weeks after ttt	1.09	0.08	1-1.34	1.07	0.09	0.8-1.3	1.17	0.24 (NS)
INR 12 weeks after ttt	1.08	0.10	0.91-1.37	1.06	0.08	0.9-1.3	1.1	0.27 (NS)
P(Repeated measures ANOVA)	0.038 (S)			0.011 (S)				
Significat pairs	Before versus 12 w			Before versus 4 w Before versus 12 w				

Table (2) There is significant decrease of ALT levels by the end of treatment and 12 weeks after treatment in comparison with ALT levels before treatment. Regarding AST, there is significant decrease of AST levels by the end of treatment and 12 weeks after treatment in comparison with AST levels before treatment. On the other hand, there is non-significant change in serum albumin, total bilirubin, INR or AFP over time.

Table (3) Comparing the studied groups regarding ultrasound findings

			Groups		**χ^2**
			HCV only group	**HIV-HCV co-Infected group**	**(P)**
Liver size	**Average**	Count	43	30	8.57
		% within Groups	86.0%	60.0%	(0.003, S)
	Hepatomegaly	Count	7	20	
		% within Groups	14.0%	40.0%	
Total		Count	50	50	
		% within Groups	100.0%	100.0%	
Liver texture	**Normal**	% within Groups	43	44	0.36 (NS)
Total	**Coarse/cirrhotic**	Count	86.0%	88.0%	
	Coarse/cirrhotic Bright	% within Groups	7	4	
		Count	14.0%	8.0%	
	Bright Count	% within Groups	0	2	
		50	0.0%	4.0%	
Total		% within Groups	100.0%	50	

Table (3) Ultra-sonographic findings sow hepatomegaly in 40% of patients of HIV-HCV co-infection group compared to 18% in patients with mono-infection group on follow up along study duration, but had no significant difference in liver parenchyma, portal vein diameter, spleen size, no presence of ascites or hepatic focal lesions.

Table (4) HCV-PCR for the whole studied patients.

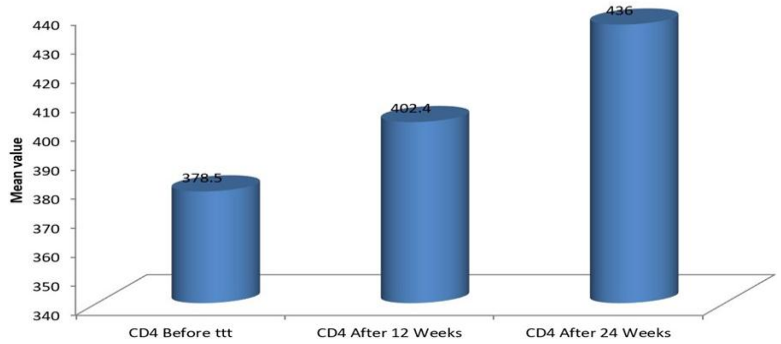
HCV-PCR before treatment	**HCV only**	**IQR 105**	2.12-30		P
		Median 105	10		0.81
	HIV-HCV co-infected	**IQR 105**	2.6-26.0		(NS)
		Median 105	9.92		
By the end of treatment 12 weeks	**HCV only**	**Number (%)**	Negative	50 (100%)	
			Positive	0 (0.00%)	
	HIV-HCV co-infected	**Number (%)**	Negative	50 (100%)	
			Positive	0 (0.00%)	
SVR at 24weeks	**HCV only**	**Number (%)**	Negative	49 (98%)	1.0 (NS)
			Positive (relapse)	1 (2%)	
	HIV-HCV co-infected	**Number (%)**	Negative	48 (96%)	
			Positive (relapse)	2 (4%)	

Table (4) There was 2 relapsed patient of group (HCV-HIV co-infected) while 1 relapsed patient in group (HCV only) with no significant difference.

Table (5) side effects between 2 groups.

Variable		**HCV only group (n=50)**		**HCV-HIV co-infected group (n=50)**		**P**
		No.	%	No.	%	35.1
Side effects	**Fatigue**	21	42.0	37	74.0	(<0.0
	Headache	18	36.0	24	48.0	01
	Insomnia	4	8.0	17	34.0	,HS)
	Relapse	1	2.0	2	4.0	
	Diarrhea	0	0.0	12	24.0	
	Nausea	0	0.0	11	22.0	
	Pruritis	0	0.0	7	14.0	

Table (5) There was significant difference between two groups as regard side effects . Group (HCV-HIV co-infected) developed more side effects when compared to othe group (HCV only), table 5



CD4 changes before and after treatment: there is significant increase of CD4 count before treatment, at the end of treatment and after 12 weeks of end of treatment.

4. Discussion

In recent years, new direct antiviral medication regimens have eliminated persistent HCV infection. [22]. High SVR rates were obtained in clinical trials and real-world cohorts with a low incidence of side events with direct antiviral regimens. [22]. Sofosbuvir and daclatasvir were used in a prospective study to evaluate the safety and efficacy of the regimen in both patients with HIV and those with HCV mono-infection. There was no statistically significant difference in baseline demographic data between the two groups, except for the higher age of HCV mono-infection, which was discovered by chance and had no symptoms, whereas HIV has common symptoms that are likely to be recued. [7]. For individuals with HIV/HCV co-infection, they reported an SVR 12 of 91% in those taking all oral DAA regimens (of whom 25% received the combination of sofosbuvir and daclatsvir). whereas Wyles et al. are near enough to us to be comparable. One research found an SVR rate of 97% in individuals with HIV and HCV co-infections treated with the same DAA combinations. The SVR

12 rate reported by Omar et al. [8] and Amr et al. [23] was 95.1 percent after following the same regiment for patients with HCV mono-infection, whereas our research revealed an SVR rate of 98 percent for HCV mono-infection.

IV drug addicts account for 64% of HIV infections, followed by illegal sex (18%), blood transfusion (14%) and IHV positive partner 8%. This shows that IV drug addicts are the primary source of HIV infection, which is similar to the findings of UNOCD [21], which found that 41% of HIV infections occurred through IV drug use.

A significant decline in the necroinflammation markers (AST and ALT) 12 weeks after the end of treatment by sofosbuvir-based regimens, as well as improvements in AST and ALT were observed in both groups of patients in our study that showed no significant differences except for ALT and AST. Elsharkawy et al. [16] and Bachofner et al. [17] concur with this finding.

Regarding the issue of security Truvada (tenofovir+emtricitabine) and efavirenz were the antiretroviral regimens of choice for all patients in our research. In addition, no patients were found to have stopped their therapy due to medication interactions between DAAs and ARVs. Our findings are backed up by Panel et al. [11], who reported that Daclatasvir and sofosbuvir both have low drug-drug interactions; there are no interactions with tenofovir, emtricitabine, rilpivirine, raltegravir or dolutegravir with these two antiretroviral medicines. Daclatasvir and sofosbuvir were not required to alter HIV therapy throughout our investigation, and we followed the advice of T. Garimella et al. [12] to provide a 90 mg dosage of daclatasvir with efavirenz. It was also well tolerated in our trial, with no reported significant adverse events and no discontinuations owing to adverse events, and the majority of events seen were classified as mild or moderate as mild or moderate as mild or moderate, respectively (fatigue 58 percent , headache 42 percent , nausea 11 percent). This is similar to what was reported by Sulkowski et al. [18], Molina et al. [19], Naggie et al. [20] and Wyles et al. [1] about the safety of DAAs in HIV/HCV co-infected patients and what was reported by Wyles et al. [1] about the safety of daclatasvir plus sofosbuvir combination in HIV/HCV co-infected patients. This is consistent with what was reported by Wyles et al. [1].

According to Wyles et al. [1] and the (ION-3 research), patients with a high baseline HCV RNA level were more likely to relapse. Serum HCV RNA load changes, which may explain why the threshold for an elevated relapse rate in Wyles et al [1] was lower than that in our research, which included three relapsed cases (14 million IU per millimetre), which may explain why these disparities were found. HCV levels in the blood are not necessarily indicative of a more active viral replication in the liver or a worsening of the patient's liver condition. HCV has been shown to multiply in the liver and in other organs [14].

Our research shows a rise. It has been shown that the CD4 count increases after SVR, and Dazley et al. [15] agree with us as they indicate a rise in CD4 count after obtaining SVR that is explained by the regression of hepatic fibroids, which may contribute to the avoidance of large amounts of spleen and liver disease. Besides chronic inflammation, which may have contributed to a lower CD4 count in the non-SVR group, another potential reason is the ongoing immunological activation and CD4 T cell death associated with HCV infection in the co-infected individuals. [15,16] When the HCV therapy is successful, this activation reduces. A large rise in CD4 count following SVR is consistent with the findings of our investigation.

5. Limitation

Despite the small sample size, short observation duration and the fact that all patients were evaluated in a single site, our research had limitations. We need more evidence on DAA treatment for patients with HCV-HIV co-infection since the number of patients is so tiny. The effectiveness and safety of DAA therapy, as well as the possibility of anti-HIV effects and CD4 count monitoring after treatment with DAAs, all need a longer observational period.

6. Conclusion

Using direct-acting antiviral medicines, we were able to obtain excellent cure rates for chronic HCV in HIV-HCV co-infected individuals. There was a high incidence of sustained virologic response (SVR) 12 weeks after therapy, AST and ALT were reduced, and CD4 count considerably raised 12 weeks after treatment. The use of DAAs has a high level of safety associated with it. There were no patients who had to stop therapy due to side effects.

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