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SAFETY AND EFFICACY OF DIRECTLY ACTING ANTIVIRAL DRUGS IN TREATMENT OF CHRONIC HCV EGYPTIAN PATIENTS

By
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Abstract

Emergence of direct antiviral agents (DAAs), and campaign done by the National Committee for Control of Viral Hepatitis (NCCVH), reduced chronic hepatitis C (CHC) prevalence in Egypt. This study evaluated the efficacy and safety of used DAAs in affiliated centers from October 2017 to December 2019. Patients were either started treatment or during follow-up for 1 year after therapy (EOT). They were divided according to treatment into GI: SOF/DAC for 12 weeks, GII: SOF/DAC/ RBV for 12 weeks, GIII: SOF/SIM for 12 weeks, GIV: SOF/RBV for 24 weeks and GV: SOF/ DAC/RBV for 24 weeks. DAAs were effective in all groups, and adverse effects occurred in 54 patients (38.6%).

The commonest complications were ascites (n=18) followed by jaundice (n=17) and HCC (n=14). Patients (97.1%) in GIV complained of adverse effects compared to others with a significant difference ($p<0.001$). Hematemesis occurred in one patient in GIV. There was also a significantly higher proportion of ascites (38.2%) in GIV compared to others ($P < 0.01$), without significant differences between groups regarding HCC and renal impairment (RI) ($P= 0.316$ & 0.758 respectively). Five treatment experienced patients suffered from side effects. Renal impairment was (12.5%) among interferon (IFN) experienced and SOF/DAC experienced patients and who were treated among GIV and GV, hepatic encephalopathy was (12.5%) in IFN experienced and SOF/RBV experienced patients among GIV or GV, but ascites (6.3%) and jaundice (6.3%) were among GIV. None complained of hematemesis or HCC.

Keywords: Egypt, Patients, Emergence of direct antiviral agents, CHC, chronic hepatitis C, DAAs.

Introduction

Egypt used to have the highest prevalence of hepatitis C virus (HCV) in the world (Abdel-Wahab *et al,* 1994). Egypt conducted a successful HCV screening program that covered more than 50 million residents and treated more than 4 million, poised to be the first world country to eliminate HCV within its borders (Hassanin *et al*, 2021). The HCV seroprevalence among untreated persons was lower than those in 2015, which reflected the effect of treatment by direct acting antivirals or DAAs (Waked *et al,* 2020).

Treatment of chronic hepatitis C (CHC) by DAAS has a great impact on liver biochemical profile in most patients. This is mostly attributed to suppression of viral replication. The improvement was also in cirrhotic patients and those who didn't achieved SVR (El-Kassas *et al,* 2021).

The cirrhosis, particularly if associated with high liver stiffness and α-fetoprotein (AFP) values, diabetes and male sex were identified as risk factors for HCC occurrence in CHC treated by DAAs attributed to reduction in immune surveillance in response to rapid clearance of HCV and changes in cytokine pattern influencing early carcinogenesis (Rinaldi *et al,* 2020). But, several studies reported that HCV treatment by DAAs was associated with decreased risk of HCC, due to the decrease of post-treatment intrahepatic inflammation by achieving SVR (Shiha *et al,* 2020). Among currently approved DAAs, Sofosbuvir® (SOF)

is the only one with significant renal elimination, though its nephrotoxicity still controversial (Jadoul and Martin, 2017).

In 2015 the National Committee for the Control of Viral Hepatitis (NCCVH) categorized CHC patients into easy to treat or difficult to treat ones. Difficult to treat patients were the Peg-FN experienced, with total serum bilirubin ≥1.2 mg/dl, serum albumin ≤3.5gm/dl, INR ≥1.2 and platelet count <150.000/mm³. Easy to treat patients were eligible to be treated by sofosbuvir/daclatasvir (SOF/DAC) for 12 weeks, while difficult to treat ones were eligible to be treated with SOF/DAC/RBV for 12 weeks up to 24 weeks treatment in patients with previous SOF failed regimen. By the year end, Simeprevir® (SIM), Ledispavir® (LED) and Paritaprevir/Ritonavir/Ombitasvir (Querevo®) were developed and easily treated patients with either SOF/DAC, SOF/SIM, SOF/LED, or (Querevo®) + RBV for 12 weeks, taken into consideration that neither SOF/SIM nor Querevo/RBV to be used in patients with Child-Pugh class B or C cirrhosis (Sabal *et al,* 2020).

Materials and Methods

Study design: A total of 140 CHC patients eligible for DAAs therapy from October 2017 to December 2019 according to the NCCVH, were selected. Patients were either started treatment or during their follow-up. The patients who were coming for follow-up were either receiving treatment or undergoing regular follow-up after end of therapy (EOT).

Regimens given were Sofosbuvir/simprevir for 12 weeks, or Sofosbuvir/daclatisvir for 12 weeks, or sofosbuvir/daclatasvir/ribavirin for 12 weeks, or sofosbuvir/ledispavir for 12 weeks, or sofosbuvir/daclatasvir/ribavirin for 24 weeks, or sofosvuvir/ribavirin for 24weeks.

Excluded patients: Patients presented during follow-up and on IFN treatment based regimens, HCC, hepatic decompensation and renal impairment that occurred before treatment.

Clinical examination: Patients were subjected to medical history taking and examination with special emphasis on history of previous CHC treatment specially its type, treatment duration and date of last dose, current co-morbidities and regular medications to avoid drug interaction, previous history of hepatic decompensation as jaundice, hematemesis or melena with any endoscopic intervention or previous paracentesis. For childbearing ones, date of last menstrual period, if she was lactating, the use of an effective contraceptive measure mainly during treatment and for 6 months after EOT for her and husband, also, examined encephalopathy, jaundice and/or ascites.

Laboratory tests: CBC, LFTs, KFTs, Pregnancy test for childbearing females, serum AFP immediately before treatment and at EOT, HBsAg, HCV-RNA PCR, evaluation of liver fibrosis using FIB-4 score. FIB-4=

$$\frac{\text{age(years)} \times \text{ASTlevel (U/L)}}{\text{Platelet count } (10^{\square}/\text{L}) \times \sqrt{\text{ALT(U/L)}}}$$

FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis. But, a FIB-4 >3.25 have a 97% specificity and a positive predictive value of 65% for advanced fibrosis (Sterling *et al,* 2006). Renal impairment was evaluated by serum creatinine and clearance by Cockcroft-Gault score.

Radiological investigations: abdominal ultrasound, dynamic imaging if any hepatic focal lesion was detected or if AFP>100ng/ml. Patients were instructed to have regular visits once started therapy and every 4 weeks to assess occurrence of any adverse effects. After EOT, they were monitored after 1 month, 3 months, 6 months and 1 year after EOT.

Ethical approval: The study was carried out according to Faculty of Medicine, Ain-Shams University ethical recommendations that agreed with the guidelines of 1975 Declaration of Helsinki (6th Revision, 2008). A written informed consent from the participated patients was obtained after explaining the study aim.

Statistical analysis: Data were analysed by Statistical Package of Social Science (SPSS)

(version 28). Stepwise logistic regression was applied to signify variables within univariate analysis using forward likelihood ratio method. Odds ratio (OR) and its 95% confidence intervals (CI) estimated the risk. A P-value less than 0.05 were considered significant.

Results

Out 140 patients, 35.7% were females and 64.3% were males. Median age was 56 years (25-73). 88.6% of the participants were naïve and 11.4% were experienced. Experienced ones (56.3%) were relapsed over SOF/RBV regimen. Most common regimens were SOF/DAC 12 weeks (34.3%) followed by SOF/RBV 24 weeks (24.3%) and SOF/DAC/RBV 12 weeks (22.9%). SVR was measured 12 weeks after EOT (SVR12) by 82 patients (58.6%), 13 patients (9.3%) didn't respond, and 45 (32.1%) didn't reach PCR assessment due to complications. Patients were 88.6% in GI, 82.1%, in GII, 85.7%, in GIII, 50%, in GIV, but all in G V achieved SVR12.

At week 4 of treatment: GI patients were Child-Pugh class A, only 97.9% remained as A & 2.1% turned to class B. GII patients, 90.6% were class A & 9.4% class B, only 87.5% remained class A & 12.5% turned to class B. GIII patients 100% were class A, only 72.2% remained class A &27.3% turned ito class B. GIV patients, 70.6% were class A & 29.3% class B, at week 4 of treatment, 38.2% remained class A, 56.9% turned to class B & 5.9% were class C. GV patients, 80% were class A & 20% class B and remained stable via treatment and follow-up. Besides, Hb was significantly lower in GII compared to GI ($P < 0.01$), and also was significantly lower in GIV compared to GI ($P<0.001$). ALT was significantly high in GIV compared to GI ($P<0.05$). AST was significantly higher in GIV compared to GI ($P< 0.05$). INR was significantly high in GIV compared to GI ($P<0.001$), & also compared GIII ($P<0.05$). Total bilirubin was significantly high in GII than GI ($P<0.01$), high in GIV than GI ($P<0.001$), and high in GV than GI ($P<0.05$). Serum albumin was significantly low in GIV than GI ($P<0.001$), GII ($P<0.01$) & GIII ($P<0.05$), with significant difference among groups. Serum creatinine was overall ($P = 0.047$).

At week 12 of treatment, Hb was significantly low in GIV than GI ($P<0.001$). ALT was significantly high in GIV than GI ($P<0.05$). AST was significantly high in GIV than GI ($P<0.001$). INR was significantly high in GIV than GI ($P<0.001$), and GII ($P<0.01$). Total bilirubin was significantly high in GIV than GI ($P<0.001$) & GII ($P<0.05$). Total bilirubin was significantly high in GV than GI ($P <0.01$). Serum albumin was significantly low in GIV than GI ($P<0.001$), GII ($P<0.05$) and GIII ($P<0.05$). Serum creatinine was significantly low in GIII than GI ($P<0.05$). FIB-4 was high significantly in GII than GI ($P < 0.01$), and in GIV than GI ($P< 0.001$). Also, GV was significantly high than GI ($P<0.01$). AFP was significantly high in GII than GI ($P <0.05$), and significantly high in GIV than GI ($P <0.01$).

Patients (n=54) suffered from ascites (18) followed by jaundice (17) and HCC (14). Renal impairment occurred in 12 patients, 7 with hepatic encephalopathy and 1 with hemateme sis. In GIV patients (97.1%) suffered from adverse effects significantly compared to others ($P <0.001$), hematemesis with high ascites proportion ($P<0.001$) and a significantly high hepatic encephalopathy (P 0.003), also a significant high jaundice proportion ($P< 0.01$), without differences among groups as to HCC & RI ($P = 0.316$ & 0.758 respectively).

At baseline at week 4 of SOF/RBV treated patients for 24 weeks, a significant decrease was in Hb ALT, AST & albumin ($P<0.001$), but increase in creatinine ($P<0.01$). Patients (97.1%) suffered from adverse effects, ascites (38.2%), jaundice (32.4%), both hepatic encephalopathy & HCC (17.6%). By regressive analysis, adverse effects patients were significantly old than others ($P<0.001$), with a significant high adverse effect among SOF/RBV treated ones ($P<0.001$), and high among those

treated 24 weeks (P <0.001). As to significant risks of adverse effects by Univariate analysis, fibrotic patients (3.25) were more than (5.106) times to adverse effects. SOF/RBV treated patients were 58.406 times more to adverse effects. Older ages was associated with more adverse effects (p=0.051).

Details were given in tables (1.2.3.4.5, & 6).

Table 1: Sociodemographic, disease and treatment history among group

Characteristic	Total (n=140)
Age (years)	
Median (range)	56 (25-73)
Sex	
Male	90 (64.3%)
Female	50 (35.7%)
Naïve	124 (88.6%)
Experienced	16 (11.4%)
Previous TTT:SOF/RBV relapse	9 (56.3%)
IFN relapse	4 (25%)
SOF/SIM relapse	1 (6.3%)
SOF/DAC relapse	1(6.3%)
SOF/RBV/IFN experienced	1(6.3%)
SOF/DAC 12wks	48 (34.3%)
SOF/RBV 24wks	34 (24.3%)
SOF/DAC/RBV 12wks	32 (22.9%)
SOF/SIM 12wks	11 (7.9%)
SOF/DAC/RBV 24wks	10 (7.1%)
SOF/DAC 24wks	3 (2.1%)
SOF/LED 12wks	1 (0.7%)
SOF/SIM 24wks	1 (0.7%)

Table 2: Blood parameters among groups at week 4 of treatment

Variable	GI	GII	GIII	GIV	GV	P value
Haemoglobin	14 (7± 16.4)	12.2 (8.7±14.2)[a]	11.6 (8.4±16.8)	11.1 (6.6±13.8)[a]	12.2 (9.5±16.7)	<0.001
ALT	21.2 (7.5±55)	21.2 (8±100)	24 (10.7±43)	29.0 (10±62)[a]	21.3 (12±35.7)	0.030
AST	23.3 (12.9±64.4)	26.6 (12-95)	24.8 (10±141)	32.2 (11.9-230.6)[a]	27.7 (15±43)	0.027
INR	1 (1±1.36)	1.1 (0.8±1.8)	1 (1±1.3)	1.1 (1±1.8)[ac]	1.1 (1±1.4)	<0.001
Bilirubin	0.7 (0.3±3)	1 (0.4±2.7)[a]	0.9 (0.5-2.6)	1.6 (0.4±2.9)[a]	1 (0.5±2.4)[a]	<0.001
Albumin	3.9 (3.1±4.9)	3.6 (2.8±4.4)	4 (2.5±4.6)	3.1 (2.5±4.1)[abc]	3.5 (2.7±4.7)	<0.001
Creatinine	1 (0.6±1.9)	0.9 (0.5±1.7)	0.9 (0.5±1.8)	1 (0.6±5.2)	0.8 (0.6±3.5)	0.047

a significantly different from SOF/DAC 12wks, b significantly different from SOF/DAC/RBV 12wks, c significantly different from SOF/SIM 12wks, d significantly different from SOF/RBV 24wks, e SOF/DAC/RBV 24 weeks

Table 3: Blood parameters among groups at week 12 of treatment.

Variable	GI	GII	GIII	GIV	GV	P value
Haemoglobin	13.8 (10.1±16.3)	11.6 (9.5±14.4)	12.7 (8.6±16)	10.4 (10.4±13.7)a	12.2 (9.8±14.1)	<0.001
ALT	18.5 (4±81)	18.1 (7.3±73.6)	21.7 (9.6±115.2)	27.2 (16±90.2)a	22 (11.4±31)	0.028
AST	22.7 (5.4±52)	25.9 (14±77.3)	32.3 (9.6±140)	40.0 (10±240)a	25 (17.5±59.6)	0.001
INR	1 (0.93±1.5)	1.1 (0.9±1.7)	1 (1.2±3.27)	1.3 (1.1±1.8)ab	1.1 (1±1.6)	<0.001
Bilirubin	0.7 (0.3±1.3)	0.9 (0.5-3.1)	0.9 (0.3±1.8)	1.7 (0.7±)ab	1.2 (0.5±1.9)a	<0.001
Albumin	4 (3.4±5.8)	3.8 (2.9±4.8)	4.1 (3.02±4.6)	3.1 (2.4±4.7)abc	3.6 (2.8±4.6)	<0.001
Creatinine	1 (0.5±1.6)	0.9 (0.5±1.4)	0.7 (0.4±2.5)a	0.9 (0.5±1.6)	0.9 (0.2-1.2)	0.008
CGS	93 (53±238)	97 (35±163)	109 (35±207)	96 (12±191)	99 (58±136)	0.837
Fib- 4	1.2 (0.3±3.1)	1.9 (0.8±8.3)a	1.6 (0.4±15.8)	3.6 (0.8-357)a	2.9 (1.4±7)a	<0.001
AFP	3.3 (1.1±28.1)	7 (1.4±400)a	4 (2±1000)	9 (2.5±220)a	6.4 (3±10.9)	0.002

Table 4: Side effects due to treatment regimen among groups.

Adverse effects	GI (n=48)	GII (n=32)	GIII (n=11)	GIV (n=34)	GV (n=10)	p-value
No	41 (85.4%)	26 (81.3%)	6 (54.5%)	1 (2.9%)	8 (80%)	
Yes	7 (14.6%)	6 (18.8%)	5 (45.5%)	33 (97.1%)	2 (20%)	<0.001
Hematemesis	0 (0%)	0 (0%)	0 (0%)	1 (2.9%)	0 (0%)	------
Ascites	0 (0%)	2 (6.3%)	2 (18.2%)	13 (38.2%)	0 (0%)	<0.001
Hepatic encephalopathy	0 (0%)	0 (0%)	0 (0%)	6 (17.6%)	1 (10.0%)	0.003
Jaundice	1 (2.1%)	4 (12.5%)	1 (9.1%)	11 (32.4%)	0 (0%)	0.002
HCC	3 (6.3%)	3 (9.4%)	2 (18.2%)	6 (17.6%)	0 (0%)	0.316
Renal impairment	3 (6.3%)	2 (6.3%)	1 (9.1%)	5 (14.7%)	1 (10.0%)	0.758

*patient < complications

Table 5: Side effects after exposure to DAAs treatment

Characteristic	Total (n=140)	No (n=86)	Yes (n=54)	p-value
Age (years)	54.9±9.3	52.7±9.7	58.5±7.7	≤0.001
Male	90	57 (63.3%)	23 (36.7%)	
Female	50	29 (58.0%)	21 (42.0%)	0.534
Naive	124	75 (60.5%)	49 (39.5%)	
Experienced	16	11 (68.8%)	5 (31.3%)	0.523
Child score A	124	83 (66.9%)	41 (33.1%)	
Child score B	16	3 (18.8%)	13 (81.2%)	≤0.001
Fibrosis ≤3.25	81	66 (81.5%)	15 (18.5%)	
Fibrosis >3.25	59	20 (33.9%)	39 (66.1%)	≤0.001
TTT SOF/DAC	51	43 (84.3%)	8 (15.7%)	
TTT SOF/DAC/RBV	42	34 (81.0%)	8 (19.0%)	
TTT SOF/SIM & SOF/LED*	13	8 (61.5%)	5 (38.5%)	
TTT SOF/RBV	34	1 (2.9%)	33 (97.1%)	≤0.001
Durations 12 weeks	92	74 (80.4%)	18 (19.6%)	
Durations 24 weeks	48	12 (25%)	36 (75%)	≤0.001
Response to treatment (n=95)**				
Positive PCR	13	12 (92.3%)	1 (7.7%)	
Negative PCR	82	74 (90.2%)	8 (9.8%)	0.813

*One patient received Sof/led,**45 patients PCR not assessed

Table 6: Multivariate analysis of factors causing adverse effects among groups

Variations	B	S.E.	P-value	OR (95%)	Lower	Upper
Fibrosis (>3.25 vs. ≤3.25)	1.630	.664	.014	5.106	1.390	18.758
TTT SOF/DAC/RBV vs. SOF/DAC	-1.019	.746	.172	.361	.084	1.558
TTT SOF/SIM & SOF/LED vs. SOF/DAC	.623	.833	0.455	1.846	.365	9.528
TTT SOF/RBV vs. SOF/DAC	4.067	1.136	<0.001	58.406	6.307	540.900
Age	.071	.036	.051	1.073	1.000	1.152

B: regression coefficient, SE: standard error

Discussion

The HCV infection was in 92.5% of Egypt patients infected with genotype 4, 3.6% with genotype 1, 3.2% with multiple genotypes, and < 1% patients with other genotypes (Kouyoumjian *et al*, 2018).

In the current study, of 140 CHC patients, 90 (64.3%) were males, and 50 (35.7%) were females, with age ranged from 25-73 years with a median of 56 years. These patients were known HCV infected men more than women in a disproportionate way. However, in chronic HCV females were more ability to spontaneously virus clearance with slower rates for disease progression than males (Baden *et al,* 2014). The HCV treatment was achieved by SVR with undetectable HCV-RNA by highly sensitive quantitative assays 12 weeks after treatment (SVR12), which highly concordant with the previous SVR24 in interferon era (Dieterich *et al,* 2015).

DAAS was developed on 2014/2015 to treat CHC giving IFN-free regimens, with shorter duration of treatment, fewer side effects and higher response (Asselah *al,* 2016). Attainment of an SVR, defined as aviremia 12 or 24 weeks after completion of antiviral therapy (SVR12 or SVR24) was associated with an improved prognosis compared to those either untreated or failed therapy (Simmons *et al,* 2015).

In the current study**,** 95 patients (67.8%) reached SVR12 assessment point, of them 82 (86.3%) achieved SVR12, but 13 (13.6%) did not. These lower percentages can be attributed to fact that only 42.2% of the total included patients were classified as "easy to treat" and were non-cirrhotics. By compared the virological response among patients, 100% of GV achieved SVR12 (80% class A at baseline), followed by 88.6% in GI (100% of class A at baseline) and 85.7% in GIII (100% class A at baseline). Higher response of groups was attributed to better baseline liver functions and Child-Pugh classification.

In the present study, the total percentage of

SVR12 was lower than in other studies, they all agreed that baseline liver functions, especially total bilirubin and serum albumin, and better Child-Pugh class were associated with better virological response. Higher baseline total bilirubin, lower baseline serum albumin and higher Child-Pugh class gave as predictive parameters for lower virological response (Welzel *et al,* 2016). They treated over 485 CHC patients, with SOF (400mg) and DAC (60mg) for 24 weeks, SVR12 was achieved in 92% of patients treated with SOF/DAC and in 89% of SOF/DAC/RBV treated patients. Also, higher rates of SVR12 were achieved with Omar *et al*. (2018) among 18378 naïve patients with or without cirrhosis, treatment experienced patients (IFN or SOF experienced). Patients were treated with SOF/DAC+/-RBV for 12 weeks, after NCCVH protocol. 95.1% achieved SVR12 (95.4% treated without RBV and 94.7% treated with RBV (P =0.32).

In this study, among patients who were treated with SOF/DAC/RBV with normal baseline laboratory tests and treated experienced, all responded, which agreed with the present study, as the patients with higher serum albumin, lower total bilirubin, FIB-4 and liver enzymes at baseline better responded to therapy. Abdel-Moneim *et al.* (2018) evaluated over 946 CHC patients for efficacy and safety of DAAs treatment, patients were classified into: G1 (easy to treat) with a dual therapy of SOF/DAC daily for 12 weeks and G2 (difficult to treat) with a triple therapy of SOF/DAC/RBV daily for 12 weeks. SVR12 was achieved by 94% (891/946) in patients, by 95% (718/758) in easy-to-treat group, and by 92% (173/188) in difficult-to-treat one.
Also, Elhammady *et al.* (2020) with over 200 Egyptian treatment naïve CHC patients, categorized into easy to treat group, treated by SOF/DAC for 12 weeks, and difficult to be treated by SOF/DAC/RBV for 12 weeks. They concluded that patients without cirrhosis exhibited higher rates of SVR compared to those with cirrhosis, but, all attained SVR12 was 93.5% (100% in easy treated and 87% in difficult treated).

In the current study, ALT 7 AST levels showed decline among all patients compared to baseline across time period. This agreed with Menesy *et al.* (2021) who reported that decline in liver enzymes was due to decrease of hepatic inflammation by viral replication suppression**.** However, with regimens given at weeks 4 & 12 of treatment, ALT & AST were significantly higher in GIV than in GI. This agreed with Elsharkawy *et al.* (2017) who reported that Egyptian CHC patients treated with SOF-based regimens, the ALT & AST levels significantly decline from baseline till 12 weeks after EOT, was a significant improvement in platelets count from baseline to SVR12 as reflected in improvement of FIB-4 score. This agreed with Fouad *et al.* (2019) who found that 456 CHC patients on DAAs showed improvement of ALT and AST from baseline to SVR 24, due to the fact that liver necro-inflammatory activity led to early improvement fibrosis and non-invasive fibrosis markers. Moreover, Ali *et al*. (2020) reported that over 240 HCV-cirrhosis patients received SOF/DAC for 24 weeks, there was a rapid decline of ALT started on 4th week of treatment and remained within normal range till 12 weeks after EOT. However, this disagreed with Morii *et al.* (2016) who found that ALT elevation during treatment was due to reduction of the inhibitory effects of HCV proteins after its eradication on adaptive immunity and had provoked immune reconstitution inflammatory syndrome. Also, this disagreed with Welsch *et al.* (2017) who found that over 493patients ALT levels despite SVR treated with different antiviral regimens, male patients showed advanced liver disease and steatosis. Besides, this disagreed with Tacke *et al.* (2020) who found that over 4946patients received DAAs, of whom 97% achieved SVR12; ALT was elevated in 67.1% in SVR12 & 79% of patients. They added that by high BMI, type 2 diabetes, alcoholism and liver cirrhosis

of the patients. In the present study, in all patients, FIB-4 decreased during treatment and follow-up, by the decline in liver enzymes. FIB-4 showed a mild rise at 6 months after EOT, and in GI even lower than the baseline due to other host factors. At week 12, FIB-4 score was higher in all than in GI, which were "easy to treat" with lowest FIB-4 at the baseline. This agreed with Bachofner *et al.* (2017) who assessed the 549 fibrosis patients scores APRI and found that patients with SVR after DAA therapy showed significant regression of transient elastography values. Also, this agreed with Mansour *et al.* (2019) who treated 200 naïve CHC patients with PEG-IFN/SOF/ RBV, SOF/RBV for 24 weeks, SOF/ DAC for 12 weeks and SOF/DAC/RBV for 12 weeks. They found that patients showed significant decline in liver enzymes, fibroscan and FIB-4 score regardless treatment response. Also, this agreed with Hsu *et al.* (2019) who found that in 395 patients declined in FIB-4 & APRI scores with therapy and remained to12 weeks after EOT. Ghoneim *et al.* (2020) found that in 343 CHC patients received DAAs; there was a significant drop in mean FIB-4 score from baseline to post-SVR ($P < 0.001$). This also agreed with Soliman *et al*. (2021) they reported among 915 CHC patients with advanced cirrhosis and fibrosis; hepatic necroinflammation were improved evidenced by decrease ALT& AST levels with increased platelet count at same period at EOT and 24-weeks after EOT (SVR24). Roh *et al.* (2021) declared that FIB-4 is the most widely used non-invasive formula for estimating the degree of liver fibrosis combined patient's age, platelets count, AST and ALT levels.

In the present study, effect of DAAs over liver functions and over Child-Pugh class was controversial. Among patients (GIV & GV) there was increase in median total bilirubin and a decline in median serum albumin with treatment, as they were cirrhotic patients with higher median total bilirubin and lower medium serum albumin at the baseline. However, the INR median levels showed treatment improvement (GIV & GII), which were difficult to treat, attributed to early recovery of liver functions with treatment. GV showed an increase in INR median level with treatment and during the follow-up period with stable Child-Pugh class. However, the present significant raise of median total bilirubin in G I compared to the baseline and treatment values could be attributed to other unknown host variables. In patients at week 4 & week 12, total bilirubin and INR were highly increased and serum albumin decreased only in GIV. This may be attributed to cirrhosis and the intake of RBV caused hemolysis andthus hyperbilirubinemia.

In the present study, all patients in GI were Child-Pugh class A at baseline, only at week 4, 1 patient (2.1%) turned into class B, in GII, 9.4% were class B at baseline and increased in week 4 to 12.5%, with increased EOT up to 12.5% of patients; at follow-up, patients were class A. In GIII, 27.3% of patients turned to class B at week 4 of treatment, In GIV, 29.3% were class B at baseline, and at week 4 of treatment, 55.9% were still class B and 5.9% changed to class C, and in GV, class B were (10%) remained as such at week 4 of treatment, and patients nearly remained the same at EOT and at 3 months after EOT. This agreed with Welzel *et al.* (2016) who treated 359/485 CHC patients with SOF/DAC and the 126 with SOD/DAC/RBV as compared with baseline and 12 weeks after EOT. They found that total bilirubin decreased by a median 0.2mg /dL, and albumin increased by 2.0 g/L at 12 weeks after EOT. Also, this agreed with Berge *et al.* (2017) who treated 90 CHC patients with different SOF-based regimens, 60 of them had RBV. All patients were Child-Pugh class A and with compensated cirrhosis, without significant improvement in Child-Pugh class, attributed to low scores at the treatment beginning. This also agreed with Ebeid *et al*. (2020), who among 100 CHC patients received SOF/DAC±RBV showed albumin decreas-

ed with treatment. Also, 94% were Child-Pugh class A; 3.3% turned to class B & 5.5 % to class C, which occurred despite SVR (100%) achievement and marked decrease in ALT & AST with consequent decrease in FIB-4. The deterioration was attributed to the decrease in serum albumin with treatment. Though in the current study, serum albumin remained stable all patients treatment duration except in GIV.

In the current study, median serum albumin showed a decrease in median values post-treatment compared to the baseline (except in GII) though all values were within normal. This agreed with Abdulhameed *et al.* (2020) reported a significant decrease in albumin levels after DAA therapy, but without clinically significant as pre- and post-treatment values were within normal range, with mean values of 4.2 &4.1 gm/l respectively. But, this disagreed with Shousha *et al.* (2018) who in 155 patients of 3 groups according to SOF/DAC/RBV, SOF/SIM, IFN/SOF/RBV treatment did n't find significant changes in bilirubin level and INR between baseline and 12 weeks post treatment.

In the present study, INR median level was stable at baseline and 12 weeks after EOT, except in GV, but total bilirubin level declined at 12 weeks after EOT compared to baseline among groups. This partly agreed with Alhaddad *et al.* (2020) who among 847 patients of five groups: non-cirrhotic (318), compensated (196), decompensated liver cirrhosis (53), post LTx (30), and 250 treatment experienced, with different DAAs with or without RBV according to NCCVH as compared values at baseline and EOT. They reported a decrease in bilirubin levels in RBV contained regimens from 1.5 to 0.9 and in RBV free regimens from 1.1 to 0.8. CPS also showed improvement 6.46 to 5.2 in RBV contained regimens, and 7.07 to 5.45 in RBV free regimens. This disagreed with Poordad *et al.* (2016) who among 60 HCV patients with cirrhosis (Child-Pugh class A, B, or C) and 53 patients with post-liver transplantation & HCV recurrence, 50/ 60 had advanced cirrhosis, Child-Pugh scores improved in 60% of them, but were unchanged in 25%, and worsened in 15%. CPS improvement was clear in class B or C disease. Also, Hanafy *et al.* (2019) evaluated efficacy and safety of DAAs on 160 patients with decompensated HCV cirrhosis for 3 months a matched with positive control of 80 patients, and follow-up to 24–31 months They found that 3-month course of DAAs led to 90% SVR with improvement in CPS and MELD scores. The present data agreed with Menesy *et al.* (2021) who among 100 patients on SOF/DAC±RBV, SOF/LED or SOF/SIM regimens, and followed-up for 6 months after treatment, reported significant improvement of INR after DAAs treatment that decreased from 1.29 to 1.22 (P = 0.012). This was explained by hepatic function improvement after therapy including coagulation factor synthesis, without significant change in serum bilirubin as improvement of total bilirubin median level after therapy. El-Sherif *et al.* (2018), with HCV decompensated cirrhosis patients given 12 or 24 weeks of treatment with LED, SOF, & RBV or VEL, SOF, and/or RBV, or 48 weeks of treatment with SOF/RBV, showed a reduction of Child-Pugh class to class A.

In the current study, 18 patients developed ascites, 13 who were naïve patients in GIV & G1 experienced patient also in GIV, 17 developed jaundice, 16 were naïve, among them 10 in GIV and 1 experienced patient in GIV. Also, 7 patients developed hepatic encephalopathy, 5 were naïve in GIV and 2 experienced patients in GIV &GV and 1 naïve in GIV developed hematemesis. Hepatic decompensation in GIV can be attributed to their nature as adverse events and mostly hepatic decompensation were more with FIB-4>3.25 and treated with SOF/RBV for 24 weeks. This agreed with Omar *et al.* (2017) reported that of 18378 CHC patients, of who 10120 were treated with SOF/DAC, and 8258 with SOF/DAC/RBV, with a total of 5 deaths due to hepatic decompensation and SOF/DAC/RBV failed.

Also, in SOF/DAC 3 patients adverse effects were hepatic decompensation and/or ascites, and in SOF/DAC/RBV 9 patients were hepatic decompensation and/or ascites. This agreed with Elbaz *et al*. (2019) who reported that patients (77.2%) of the were naïve patients eligible for SOF/DAC±RBV, 2 with hepatic encephalopathy, 1 with hematemesis and 2 patients developed spontaneous bacterial peritonitis (SBP).

In the current study, 6 patients in **G**III developed hepatic decompensation, which agreed with Saxena *et al.* (2015), treated 160 patients with SIM/SOF±RBV & 56 received RBV, hepatic decompensation occurred in 14 patients, 7 in classes B/C, 2 in class A had hepatic encephalopathy, 3 class B/C, 1 in class A had ascites & 1 class B/C had variceal bleeding. This agreed with Reddy *et al.* (2017), treated 220 patients with SOF/SIM (61/103 experienced), SOF/SIM/RBV (20/32) or SOF/RBV (16/85), 43 patients suffered from decompensating events, one with more than an adverse event, 24 patients in SOF/RBV (19 hepatic encephalopathy, 8 ascites, 3 SBP & 3 variceal bleeding), 11 were in SOF/SIM (8 hepatic encephalopathy & 5 ascites) & 8 patients in SOF/SIM/RBV (7 hepatic encephalopathy & 1 ascites). But, this disagreed with Zeuzem *et al.* (2014) reported that in SOF/RBV, 58% were experienced and 21% were cirrhosis, SVR attained in 93% without serious adverse. Doss *et al.* (2015) among 103 patients, 52% were experienced, and 17% had cirrhosis at baseline, 90% achieved SVR12, & 63% of cirrhotic achieved SVR12, only dyspnea & isc haemia as serious adverse. Alian *et al.* (2020) 40 patients on SOF/DAC±RBV, none was hepatic decompensation. Ruiz *et al.* (2021) with 27 patients SOF/DAC, SOF/RBV, SOF/LED, SOF/ VEL none was hepatic decompensation.

In the current study, 124 patients were naïve and 16 experienced. Adverse effects occurred in 54 (38.57%), 14 naïve (25.9%) developed HCC, 6 were in GIV, 3 in GI, 3 in GII & 2 in GIII. This agreed with Kozbial *et al.* (2016); Conti *et al.* (2016); Cardoso *et al.* (2016); Reig *et al.* (2016); Kanwal *et al.* (2017); Ravi *et al.* (2017) & Calvaruso *et al.* (2018) reported that DAA therapy increased risk of *de novo* HCC as more-than-expected developed HCC, but rapid viral clearance with DAAs reduced cancer immune surveillance and anti-tumor activity. El Kassas *et al.* (2019) didn't accept hypothesis that exposure to DAAs for a long time paved the way to HCC.

In the current study, medium serum creatinine showed a significant increase in GIV at week 4. In GI & GII, CGS was significantly lower at EOT compared to baseline, but both levels remained normal. The renal impairment was identified by increased creatinine level >1.2mg/dl in 12 patients, 10 were naïve (5 in **G**IV, 3 in **G**I, 2 in **G**II, and 1 in each of GIII & GV), 2 patients were 1 in **G**IV & 1 in **G**V. Kwo and Badshah (2015) theoretically reported that SOF was only DAA with significant renal elimination without need dose adjustment, even in CKD or haemodialysis patients. Liu *et al.* (2020) among 481 patients with compensated liver diseases and eGFR ≥30 ml/min/ $1.73m^2$, received SOF-based (308) or SOF-free (173) DAAs for 12 weeks, and follow-up for 24 weeks after EOT reported that they received SOF-based DAAs experienced a significant on-treatment decline in eGFR and off-treatment improvement compared to patients receiving SOF-free DAAs. But, Chen *et al.* (2017) with 43 CHC patients DAAs treated, EOT, eGFR level was significantly decreased and serum creatinine and uric acid levels significantly increased, none was non-cirrhotic or cirrhotic with decreased eGFR levels and increased serum creatinine levels at 24 weeks post-treatment, eGFR and serum creatinine levels significantly improved only in non-cirrhotic patients. Sise *et al.* (2020) found that for the HCVs DAA therapy, CKD infection progress slowly.

Conclusion

The outcome results showed that SOF/RBV treatment for 24 weeks was associated with many hazards and used with caution. Also,

older aged patients, CP-B, 24 weeks of treatment and FIB-4>3.25 were at risk factors for developing adverse events.

References

Abdel-Moneim A, Aboud A, Abdel-Gabaar M, *et al,* 2018: Efficacy and safety of sofosbuvir plus daclatasvir with or without ribavirin: Large real-life results of patients with chronic hepatitis C genotype 4. Hepatol. Int. 12, 4:348-55

Abdel-Wahab, MF, Zakaria, S, Kamel, M, *et al,* 1994: High seroprevalence of hepatitis C infection among risk groups in Egypt. Am. J. Trop. Med. Hyg. 51, 5:563-7

Abdulhameed, NI, Aleem, MSA, Shatat, M, *et al,* 2020: Changes in serum lipid profiles and apolipoprotein levels during therapy with DAAS in Egyptian Patients infected with hepatitis c virus genotype 4. J. Crit. Rev. 7, 10:3174-8.

Agrawal, P, Gautam, A, Pursnani, N, *et al,* 2018: A comparative analysis of formulae used for the estimation of glomerular filtration rate to determine the kidney function test in patients with chronic kidney disease. J. Integr. Nephrol. Androl.5:49-53

Ahn, DG, Kim, HJ, Kang, H, *et al,* 2016: Feasibility of α-fetoprotein as a diagnostic tool for hepatocellular carcinoma in Korea. Korean J. Intern Med. 31, 1:46-53.

Alhaddad, O, Wahb, A, Sabry, A, *et al,* 2020: Role of ribavirin in the Era of direct–acting antiviral therapies of chronic hepatitis C. Expert. Rev. Anti-Infect. Thera. 18, 8: 817-22.

Alian, S, Wahba, M, Gomaa, AF, *et al,* 2020: The efficacy and safety of direct-acting antiviral drugs in the management of hepatitis C virus-related arthritis. Egypt. Rheumatol. Rehbil. 47:16-9.

Asselah, T, Boyer, N, Saadoun, D, *et al,* 2016: Direct-acting antivirals for the treatment of hepatitis C virus infection: optimizing current IFN-free treatment and future perspectives. Liver Int. 36, 1: S47-57.

Bachofner, JA, Valli, P, Kröger, A, *et al,* 2017: Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int. 37, 3:369-76.

Baden, R, Rockstroh, JK, Buti, M, 2014: Natural history and management of hepatitis C: Does sex play a role? J. Infect. Dis. 209, 3:S81-5.

Berge, E, Arencibia, A, Otón, E *et al,* 2017: Clinical outcomes of direct-acting antiviral therapy in patients with compensated hepatitis C virus-related cirrhosis. Hepatom. Res. 3:209-14.

Calvaruso, V, Cabibbo, G, Cacciola, I, *et al,* 2018: Incidence of hepatocellular carcinoma in patients with HCV-associated cirrhosis with direct-acting antiviral agents. Gastroenterology 155: 411-21.

Cardoso, H, Vale, AM, Rodrigues, S, *et al,* 2016: High incidence of hepatocellular carcinoma following successful interferon-free antiviral therapy for hepatitis C associated cirrhosis. J. Hepatol 65, 5:1070-1.

Conti, F, Buon, F, Scuteri, A, *et al,* 2016: Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J. Hepatol. 65:722-33.

D'Amico, G, Bernardi, M, Angeli, P, 2022: Towards a new definition of decompensated cirrhosis. J. Hepatol. 76, 1:202-7.

Delanaye, P, Cavalier, E, Pottel, H, 2017: Serum Creatinine: Not so simple! Nephron 136, 4:302-8.

Dieterich, D, Bacon, B, Flamm, S, *et al,* 2015: Final evaluation of 955 HCV patients treated with 12 week regimens containing sofosbuvir +/- simeprevir in the TRIO network: Academic and community treatment of a real-world, heterogeneous population. J. Hepatol. 62:S621-6.

Doss W, Shiha G, Hassany M, *et al,* 2015: Sofosbuvir plus ribavirin for treating Egyptian Patients with hepatitis C genotype 4. J. Hepatol. 63, 3:581-5.

Ebeid BA, Muhammed AA, Abd Elkareem SA, *et al,* 2020: Predictive value & changes in Child-Pugh score in chronic hepatitis C cirrhotic patients treated with direct acting antiviral agents. Egypt. J. Med. Res. 1, 2:61-74.

El Kassas, M, Alboraie, M, El-Sayed, M, *et al,* 2021: Effect of disease stage and treatment outcomes on the dynamics of liver functions during and after treatment of hepatitis C with directly acting antivirals. Eur. J. Gastroenterol. Hepatol. 33, 1: e302-7.

El Kassas M, Elbaz T, Salaheldin M, *et al,* 2019: Impact of treating chronic hepatitis C infection with direct-acting antivirals on the risk of hepatocellular carcinoma, the debate continues: A mini-review. J. Adv. Res.17:43-8.

Elbaz, T, Abdo, M, Omar, H, *et al,* 2019: Efficacy and safety of sofosbuvir and daclatasvir with or without ribavirin in elderly patients with chronic hepatitis C virus infection. J. Med. Virol. 91, 2: 272-7.

Elhammady D, Nasser M, Eissa S, *et al,* 2020: Pretreatment serum alpha fetoprotein and its relation to sustained virologic response in patients with chronic HCV infection treated with direct-acting antiviral therapy. Med. J. Viral Hepat. 4, 2: 269-73.

El-Sherif, O, Jiang, ZG, Tapper, EB, *et al,* 2018: Baseline factors associated with improvements in de-compensated cirrhosis after direct-acting antiviral therapy for hepatitis C virus infection. Gastroenterology 154, 8:e2111-21.

Fargo, M, Grogan, S, Saguil, A, 2017: Evaluation of Jaundice in Adults. Am. Fam. Physician 95:164-8

Ghoneim, S, Butt, MU, Trujillo, S, *et al,* 2020: FIB-4 regression with direct-acting antiviral therapy in patients with hepatitis C infection: A safety-net hospital experience. Front. Med. (Lausanne); 7:359-66.

Hanafy, A, Bassiony, M, Basha, M, 2019: Management of HCV-related decompensated cirrhosis with direct-acting antiviral agents: who should be treated? Hepatol. Int. 13, 2:165-72.

Hassanin, A, Kamel, S, Waked, I, *et al,* 2021: @Egypt's Ambitious Strategy to Eliminate Hepatitis C Virus: A Case Study Global Health: Science and Practice 9, 1:187-200

Hsu, WF, Lai, HC, Su, WP, *et al,* 2019: Rapid decline of noninvasive fibrosis index values in patients with hepatitis C receiving treatment with direct-acting antiviral agents. BMC Gastroenterol. 19, 1:63-8.

Jadoul, M, Martin, P, 2017: Hepatitis C treatment in chronic kidney disease patients: The kidney disease improving global outcomes perspective. Blood Purif. 43, 1/3:206-9.

Kanwal F, Kramer J, Asch SM, *et al,* 2017: Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 153:996-1005..

Kouyoumjian, SP, Chemaitelly, H, Abu-Raddad, LJ, 2018: Characterizing hepatitis C virus epIdemiology in Egypt: Systematic reviews, meta-analyses, and meta-regressions. Sci. Rep. 8, 1: 1661-8.

Kozbial, K, Moser, S, Schwarzer, R, *et al,* 2016: Unexpected high incidence of hepatocellular carcino-ma in cirrhotic patients with sustained virologic response following interferon free direct-acting antiviral treatment. J. Hepatol. 65, 4:856-8.

Kwo P, Badshah M, 2015: New hepatitis C virus therapies: drug classes and metabolism, drug interactions relevant in the transplant settings, drug options in decompensated cirrhosis, and drug options in end-stage renal disease. Curr. Opin. Organ. Transplant. 20, 3:235-41.

Mansour, RH, Zaky, S, El Kassas, M, *et al,* 2019: Evaluating the effect of direct-acting agents on liver fibrosis, by real-time elastography, fibroscan and FIB4 score in chronic HCV patients. Sci. J. Al-Azhar Med. Fac. Girls 3:237-45

Menesy A, Ehab A, Abbas N, 2021: Impact of direct-acting antiviral agents treatment on body mass index and lipid profile in Egyptian Chronic Hepatitis C patients. Med. J. Viral Hepatitis 5, 2: 21-6.

Omar, H, El Akel, W, Elbaz, T, *et al,* 2018: Generic daclatasvir plus sofosbuvir, with or without ribavir-in, in treatment of chronic hepatitis C: Real-world results from 18 378 patients in Egypt. Aliment Pharmacol. Ther. 47, 3:421-31.

Poordad F, Schiff E, Vierling JM, *et al,* 2016: Daclatasvir with sofosbuvir and ribavirin for HCV infection with advanced cirrhosis or post-liver transplant recurrence. Hepatology 63:1493-505.

Ravi S, Axley P, Jones D, *et al,* 2017: Unusually high rates of hepatocellular carcinoma after treatment with direct-acting antiviral therapy for hepatitis c related cirrhosis. Gastroenterology 152, 4: 911-2.

Reddy KR, Lim JK, Kuo A, *et al,* 2017: All-oral direct-acting antiviral therapy in HCV-advanced liver disease is effective in real-world practice: Observations through HCV-TARGET database. Aliment. Pharmacol. Ther. 45, 1:115-26.

Reig M, Mariño Z, Perelló C, *et al,* 2016: Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J. Hepatol. 65, 4:719-26.

Rinaldi L, Nevola R, Franci G, *et al,* 2020: Risk of hepatocellular carcinoma after HCV clearance by direct-acting antivirals treatment predictive factors and role of epigenetics. Cancers (Basel) 12, 6:13519.

Roh YH., Kang BK, Jun DW, *et al,* 2021: Role of FIB-4 for reassessment of hepatic fibrosis burden in referral center. Sci. Rep. 11:13616-21.

Ruiz I, Fourati S, Ahmed-Belkacem A, *et al,* 2021: Real-world efficacy and safety of direct-acting anti-viral drugs in patients with chronic hepatitis C and inherited blood disorders. Euro J. Gastroenterol. Hep-atol. 33, 1:S191.

Sabal A, Omar H, El-Taher S, *et al,* 2020: Efficacy of 24-week treatment with sofosbuvir/ daclatasvir/ribavirin in chronic hepatitis C virus-infected Egyptian Patients with previous sofosbuvir-based treatment failure. Sci. J. Al-Azhar Med. Fac. Girls 4:474-81

Saxena V, Nyberg L, Pauly M, *et al,* 2015: Safety and efficacy of simeprevir/sofosbuvir in hepatitis C-infected patients with compensated and decompensated cirrhosis. Hepatology 62, 3:715-25.

Shiha G, Mousa N, Soliman R, *et al,* 2020: Incidence of HCC in chronic hepatitis C patients with advanced hepatic fibrosis who achieved SVR following DAAs: A prospective study. J. Viral Hepat. 27, 7:671-9.

Shousha H, Abdelaziz R, Azab S, *et al,* 2018: Effect of treatment with direct acting antivirals on body mass index and hepatic steatosis in chronic hepatitis C. J. Med. Virol. 90, 6:1099-105.

Simmons B, Saleem J, Heath K, *et al,* 2015: Long-term treatment outcomes of patients infected with hepatitis C virus: A systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. Clin. Infect. Dis. 61, 5:730-40.

Singal A, Lim J, Kanwal F, *et al,* 2019: AGA Clinical practice update on interaction between oral direct-acting antivirals for chronic hepatitis c infection and hepatocellular carcinoma: Expert review. Gastroenterology156, 8:2149-57.

Sise M, Chute D, Oppong Y, *et al,* 2020: Direct-acting antiviral therapy slows kidney function decline in patients with hepatitis C virus infection and chronic kidney disease. Kidney Int. 97, 1:193-201.

Soliman Z, El Kassas M, Elsharkawy A, *et al,* 2021: Improvement of platelet in thrombocytopenic HCV patients after treatment with direct-acting antiviral agents and its relation to outcome. Platelets 32, 3:383-90.

Sterling RK, Lissen E, Clumeck N, *et al,* 2006: Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/ HCV co-infection. Hepatology 43:1317-25.

Waked I, Esmat G, Elsharkawy A, *et al,* 2020: Screening and treatment program to eliminate hepatitis C in Egypt. N. Engl. J. Med. 382, 12:1166-74.

Welzel T, Petersen J, Herzer K, *et al,* 2016: Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut 65, 11: 1861-70.

Worboys P, Wong S, Barriere S, 2015: Pharmacokinetics of intravenous telavancin in healthy subjects with varying degrees of renal impairment. Eur. J Clin. Pharmacol. 71, 6:707-14.

Zeuzem S, Jacobson IM, Baykal T, *et al,* 2014: Retreatment of HCV with ABT-450/rombitasvir and dasabuvir with ribavirin. N. Engl. J. Med. 370:1604-14