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Efficacy of antiviral therapy in patients with post-hepatitis C liver cirrhosis: is hyperuricaemia a potential adverse effect?

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ABSTRACT

Hepatitis C virus (HCV) related liver cirrhosis is considered a major health problem; sofosbuvir (SOF)/ledipasvir (LDV) and SOF/daclatsvir (DACLA) are very promising direct antiviral agents (DAAS) especially in treating HCV genotype 4 which is the main genotype in Egypt. Uric acid elevation was reported in many systemic diseases and might be elevated during direct antiviral therapy. The aim is to evaluate efficacy and safety of SOF/LDV and SOF/DACLA plus ribavirin in treating HCV related child A liver cirrhosis and assess hyperuricaemia as a potential adverse effect to this regimen.

Methods This prospective observatinal study included 128 HCV naive child A cirrhotic patients divided into two groups (77 patients were treated with SOF 400 mg, DACLA 60 mg and ribavirin 600 mg and 51 patients were treated with SOF 400 mg, LDV 90 mg and ribavirin 600 mg) for 12 weeks, during the treatment complete blood count, creatinine, bilirubin, alanine transaminase, aspartate transaminase and serum uric acid were monitored, HCV RNA quantitative PCR at 12 weeks after the end of treatment was done.

Results Response to treatment in SOF/LDV (sof/led) group is about (98%), response to treatment in SOF/DACLA (sof/dacla) group is about (96%). Hyperuricaemia was noticed in 17.6% of patients received sof/led and in 15.5% of those received sof/dacla.

Conclusion SOF+LDV and SOF+DACLA plus ribavirin regimens are highly effective in treating chronic HCV patients with compensated liver cirrhosis. Hyperuricaemia is considered a potential adverse effect to DAAS containing ribavirin and may lead to serious side effects such as renal impairment.

Summary box

What is already known about this subject?

- Sofosbuvir (SOF)/ledipasvir (LDV) and SOF/daclatsvir (DACLA) are very promising direct antiviral agents (DAAS) especially in treating hepatitis C virus (HCV), uric acid elevation was reported in many systemic diseases and might be elevated during direct antiviral therapy.

What are the new findings?

- SOF+LDV and SOF+DACLA plus ribavirin regimens are highly effective in treating chronic HCV patients with compensated liver cirrhosis. Hyperuricaemia is considered a potential adverse effect to DAAS containing ribavirin.

How might it impact on clinical practice in the foreseeable future?

- Assesment of serum uric acid should be put in mind during direct antiviral therapy in HCV related liver cirrhosis.

INTRODUCTION

There are about 185 million worldwide or more are infected with chronic hepatitis C virus (HCV), which is considered a major cause of chronic liver disease and its life threatening complications which include liver cell failure, portal hypertension and hepatocellular carcinoma within 10–30 years.[1]

HCV genotype 4 (GT 4) infection is common in the Middle East, Northern Africa and SubSaharan Africa. The highest prevalence of HCV infection is present in Egypt, with 92.5% of patients infected with GT 4.[2] The latest Demographic Health Survey in 2015 reported a seroprevalence of 10% and viraemic prevalence of 7%. Aiming to eradicate HCV infection by 2030, a national treatment programme for mass treatment of HCV in Egypt was achieved by Egyptian ministry of health using recent direct antiviral regimens.[2]

Infection with HCV is sometimes linked to the presence of extrahepatic manifestations including different metabolic abnormalities, like insulin resistance, metabolic syndrome and lipid disorders. However, the association of chronic hepatitis C with serum uric acid has not been frequently investigated.[3 4] But some studies reported that uric acid might

be useful as a predictive factor for response to pegylated interferon plus ribavirin therapy for chronic hepatitis C.[4] Uric acid is the purine metabolism end product and is further metabolised by muscles, liver and the intestines.[5] Elevated uric acid is assosciated with many systemic diseases such as cardiovascular, renal or liver diseases.[6] It is proved and concluded that sofosbuvir (SOF) and daclatsvir (DACLA) are effective in treatment of chronic HCV GT 4 infections with minimal adverse events. Pretreatment liver chemistry does not seem to correlate with treatment outcome.[7]

In October 2014, a combination of SOF 400 mg with ledipasvir (LDV) 90 mg as a single pill (Harvoni) was approved by the US Food and Drug Administration as a treatment against chronic HCV, LDV is an NS5A replication inhibitor which is most active against GT 1 and GT 4.[8] Our study aims to evaluate efficacy and safety of SOF/LDV and SOF/DACLA plus ribavirin in treating HCV related child A liver cirrhosis and assess hyperuricaemia as a potential adverse effect to this regimen.

SUBJECTS AND METHODS

This prospective observational study included 128 patients of chronic HCV infection and liver cirrhosis who presented at hepatology outpatient clinic, tropical medicine department, Minya University Hospital, Minya, Egypt, in the period from December 2018 to January 2020. Patients were collected according to the following inclusion criteria HCV RNA positivity, age 18–75 years, and treatment-naïve cirrhotic patients child A classification. Patients were excluded from the study if they had any of the followings: treatment experienced patients, patients with current or previously treated hepatocellular carcinoma, extrahepatic malignancy, liver transplanted patients, patients with severe extrahepatic manifestations, pregnancy, or inability to use effective contraception, and poorly controlled diabetes mellitus(DM); HbA1c should be below 9%, patients suffering from advanced renal disease defined by estimated glomerular filtration rate (eGFR) below 30 mL/min, patients with child B or C, patients with platelet count less than 50x10^9/L, coinfected patients either with hepatitis B virus infection or HIV virus infection or if they were receiving current drugs causing hyperuricaemia. All patients were subjected to full medical history including treatment of current chronic medical comorbid diseases, meticulous clinical examination, calculation of body mass index (BMI) and laboratory parameters including HCV antibodies using the ELISA technique, HCV RNA quantitative PCR before treatment, follow-up at the end of treatment and at 12 weeks after the end of treatment, liver function tests including aspartate aminotransferase, alanine amino transferase, prothrombin time, international normalised ratio, serum albumin and total and direct serum bilirubin, in addition to HBsAg, HIV antibody by ELISA, complete blood count, fasting blood glucose and HbA1c (in diabetic patients), serum uric acid, serum creatinine, calculation of estimated glomerular filtration rate,[9] alpha fetoprotein, pregnancy test for women in the childbearing period, and pelvi-abdominal ultrasonography. liver cirrhosis was diagnosed by clinical, laboratory parameters including Fib 4 more than 3.25[10] and ultrasongraphic characters of liver cirrhosis and portal hypertension, child pough classification was applied as mentioned.[11] HCV genotyping was done by direct sequencing of the 50 untranslated regions, using RT-PCR-based assay (AmpliSens HCV-genotype-FRT PCR kit).

Patients were treated either with SOF 400 mg, DACLA 60 mg and ribavirin 600 mg their number was 77 or with SOF 400 mg, LDV 90 mg and ribavirin 600 mg their number was 51, for 12 weeks. During the treatment complete blood count, s.creatinine, s.bilirubin, aspartate aminotransferase, alanine amino transferase and s.uric acid were monitored every 4 weeks. HCV RNA quantitative PCR at 12 weeks after the end of treatment was done. Written informed consent was obtained from all patients for both participation in the study and publication of the data.

The collected data were inserted, tabulated and statistically anatomised using SPSS software V.24. Qualitative data were expressed as proportions, while quantitative data were expressed as mean±SD. Statistical significance was defined as p values less than 0.05.

RESULTS

The present prospective study included 128 patients suffering of HCV and compensated liver cirrhosis divided into two groups 77 patients received sof/dacla/riba, and 51 patients received sof/led/riba. Table 1 shows baseline characters of the studied groups; age of sof/led group is ranging from 33 to 66 years, its mean is 53.1 and age of sof/dacla group is ranging from 36 to 69 years and its mean is 50.6, men to women ratio was 58.8% versus 41.2% in sof/led group and 54.5% versus 45.5% in sof/dacla group, the BMI of sof/led group is ranging from 23 to 36, mean is 29.9 and that of sof dacla group is ranging from 23 to 35, mean is 28.6. In sof/led group 51% of patients are rural versus 49% are urban, in sof/dacla group 50.6% of patients are rural versus 49.4% are urban, 16 patients in sof/led group (31.4%) are suffering from comorbid diseases versus 29 patients (37.7%) in sof dacla group; in the form of 3 patients suffering from hypertension (5.9%) in sof/led group versus 5 patients (6.5%) in sof/dacla group, 7 patients are diabetic (13.7%) in sof/led group versus 11 patients (14.3%) in sof/dacla group, 3 patients are diabetic and hypertensive (5.9%) in sof/led group versus 7 patients (9.1%) in sof/dacla group, 3 patients have history of gout in sof/led group (5.9%) versus 6 patients (7.8%) in sof/dacla group, 35 patients (68.6%) are free of comorbid diseases in sof/led group while 48 ones (62.3%) in sof/dacla group, no significant statistical changes between sof/led group or sof/dacla group as regard baseline characteristic data. Table 2

Table 1 Demographic data

		SOF LED	SOF DACLA	
		N=51	N=77	P value
Age	Range	33–66	36–69	0.077
	Mean±SD	53.1±8.3	50.6±7.8	
Sex	Male	30 (58.8%)	42 (54.5%)	0.633
	Female	21 (41.2%)	35 (45.5%)	
Body mass index (BMI)	Range	23–36	23–35	0.562
	Mean±SD	29.9±2.8	28.6±2.6	
Residence	Rural	26 (51%)	39 (50.6%)	0.971
	Urban	25 (49%)	38 (49.4%)	
Comorbid diseases	No	35 (68.6%)	48 (62.3%)	0.466
	Yes	16 (31.4%)	29 (37.7%)	
Comorbid diseases	Hypertension	3 (5.9%)	5 (6.5%)	0.961
	Diabetes	7 (13.7%)	11 (14.3%)	
	Hypertension and diabetes	3 (5.9%)	7 (9.1%)	
	History of gout	3 (5.9%)	6 (7.8%)	
	Free	35 (68.6%)	48 (62.3%)	

Independent samples t-test for parametric quantitative data between the two groups.
χ^2 test (if less than 20% of cells have expected count <5) or Fisher exact test (if more than 20% of cells have expected count <5) for qualitative data between the two groups.
Significant level at p value <0.05.
DACLA, daclatsvir; LED, ledipasvir; SOF, sofosbuvir.

shows that response to treatment in sof/led group is about (98%), one patient stopped treatment in the last month due to marked hyperuricaemia and subsequent renal impairment (2%), this patient fortunately showed sustained virological response (SVR). Response to treatment in sof/dacla group is about (96%), also one patient stopped treatment in the last month due to marked hyperuricaemia and subsequent renal impairment (1.3%) and fortunately had SVR, no significant difference between sof/led and sof/dacla groups regarding response to treatment (p value >0.05). Table 3 shows adverse effects occurring in both groups during treatment; headache (0% vs 1.2 %), fatigue (3.9% vs 2.6%), lower gastrointestinal tract (GIT) symptoms (1.9% vs 3.6%), upper GIT symptoms (3.9 vs 2.6%), itching (1.9% vs 2.6%), chest symptoms (1.9% vs 1.2%), anaemia (1.9% vs 2.6%), hyperuricaemia; men >7 and women >6.5 (17.6% vs 15.6%), and renal impairment due to marked hyperuricaemia (2% vs 1.3%), respectively, but no fever or severe manifestation like development of ascites, hepatic encephalopathy or GIT haemorrhage in both groups, no significant difference between sof/led and sof/dacla groups regarding adverse effects (p value >0.05). Table 4 shows that there are no significant statistical changes between sof/led group and sof/dacla group in the different laboratory parameters; alanine transaminase, aspartate transaminase, creatinine, bilirubin, albumin, INR, platelet count or uric acid either before or at the end of treatment (p value >0.05). Table 5 shows that hyperuricaemia (men >7, women >6.5) at the end of treatment occurs in about 21 cirrhotic patients (16.5%) out of 128 cirrhotic patients receiving treatment, 9 patients in sof/led group out of 51 (17.6%) while 12 patients in sof/dacla group out of 77 (15.6%), regarding

Table 2 Response to treatment

		SOF LED	SOF DACLA	
		N=51	N=77	P value
Response	SVR	50 (98.03%)	74 (96.1%)	0.275
	Relapse	1 (1.97%)	3 (3.9%)	
Treatment	Completed	50 (98%)	76 (98.7%)	1
	Stopped in the last month due to marked hyperuricaemia	1 (2%)	1 (1.3%)	

Fisher exact test (more than 20% of cells have expected count <5) for qualitative data between the two groups.
Significant level at p value <0.05.
DACLA, daclatsvir; LED, ledipasvir; SOF, sofosbuvir; SVR, sustained virological response.

Table 3 Adverse effects during treatment

	SOF LED N=51	SOF DACLA N=77	P value
Headache	0	1 (1.2%)	0.072
Fatigue	2 (3.9%)	2 (2.6%)	0.413
Lower GIT symptoms	1 (1.9%)	2 (2.6%)	0.126
Upper GIT symptoms	2 (3.9%)	3 (3.8%)	0.467
Itching	1 (1.9%)	2 (2.6%)	0.126
Fever	0	0	
Chest symptoms	1 (1.9%)	1 (1.2%)	0.765
Abdominal pain	2 (3.9%)	2 (2.6%)	0.413
Ascites	0	0	
Hepatic encephalopathy	0	0	
GIT haemorrhage	0	0	
Haemoglobin drop below 100 g/L	1 (1.9%)	2 (2.6%)	0.126
Drop of white cell count below 3×10^9/L	0	0	
Hyperuricaemia	9 (17.6%)	12 (15.6%)	0.189
Renal impairment due to hyperuricaemia	1 (2%)	1 (1.3%)	1
Total	20 (39.2%)	28 (36.2%)	0.523

Independent samples t-test for parametric quantitative data between the two groups.
χ^2 test (if less than 20% of cells have expected count <5) or Fisher exact test (if more than 20% of cells have expected count <5) for qualitative data between the two groups.
Significant level at p value <0.05.
DACLA, daclatsvir; GIT, gastrointestinal tract; LED, ledipasvir; SOF, sofosbuvir.

sex there is significant difference between patients having hyperuricaemia and those without as there is male predominance in those having hyperuricaemia (81%) versus 19% women, BMI is significantly higher in those having hyperuricaemia than those without hyperuricaemia (p value <0.05), regarding comorbid diseases, in patients with hyperuricaemia at the end of treatment there are two patients (9.5%) did not have any comorbid disease while 19 patients 90.5% have comorbid disease in the form of 1 patient is hypertensive 4.8 %, 4 patients are diabetic 19%, 6 patients are diabetic and hypertensive 28.6%, 8 patients had history of Gout 38.1% with significant statistical difference (p value <0.05). Patients with hyperuricaemia had significant higher serum uric acid level before treatment than patients without (p value <0.05). Patients with hyperuricaemia at the end of treatment had significant higher serum creatinine level before treatment than patients without (p value <0.05), also, patients with hyperuricaemia at the end of treatment had significant higher serum creatinine level after treatment than patients without (p value <0.05). Table 6 shows that by using simple logistic regression analysis hyperuricaemia is significantly related to male gender, higher BMI, presence of comorbid diseases, level of serum uric acid before treatment, level of serum creatinine before treatment and level of serum creatinine after treatment (p value <0.05), by multiple logistic regression analysis, occurrence of hyperuricaemia is significantly related to higher BMI and level of serum uric acid before treatment (p value <0.05).

DISCUSSION

By the development of different recent direct antiviral drugs regimens, chronic HCV infection came to an end.[12] Direct antiviral drugs regimens achieved high SVR rates with a low frequency of adverse effects in clinical trials and real-world cohorts.[12] The current prospective study was designed to study the efficacy of SOF/LDV plus ribavirin 600 and SOF/DACLA plus ribavirin 600 in management of Egyptian patients with HCV induced child A liver cirrhosis and assess hyperuricaemia as a potential adverse effect which may lead to serious sequel and stoppage of treatment. There was no significant statistical difference regarding baseline demographic data between the two studied groups. The rate of SVR in our study was about 98% in patients received sof led riba only one patient did not achieve SVR despite the compliance to treatment, one patient, male, 67 years old had history of gout of 30 years stopped treatment in the last 2 weeks due to marked hyperuricaemia; as the serum uric acid reached 22 mg/dL and subsequent renal affection as serum creatinine reached 5.1 mg/dL the patient was admitted to hospital and received medical treatment in the form of intravenous fluids and uric acid lowering drugs, patient improved within days and fortunately had SVR. In patients received sof/dacla/riba, the rate of SVR was

Table 4 Laboratory data in both groups before ttt and at end of ttt

		SOF LED	SOF DACLA	
		N=51	N=77	P value
Uric acid before ttt	Mean±SD	4.9±1.2	4.6±1.08	*0.1135*
	Median	5	4.1	
	IQR	4–6	4–5	
Uric acid end of ttt	Mean±SD	6.1±3.1	5.6±2.6	*0.100*
	Median	5	4.8	
	IQR	4.5–6	4–5.5	
ALT before ttt	Median	53	58	*0.170*
	IQR	47–65	47–74	
ALT end of ttt	Median	28	28	*0.119*
	IQR	25–29	26–30	
AST before ttt	Median	59	67	*0.053*
	IQR	49–75	53.5–86	
AST end of ttt	Median	31	34	0.055
	IQR	28–33	29.5–37.5	
Creatinine before ttt	Mean±SD	0.98±0.21	0.95±0.19	*0.320*
	Median	1	0.9	
	IQR	0.8–1.1	0.8–1	
Creatinine end of ttt	Mean±SD	1.12±0.61	1.11±0.56	*0.649*
	Median	1	1	
	IQR	0.9–1.1	0.9–1	
Platelets before ttt	Median	101	110	*0.063*
	IQR	87–123	95.5–126	
Platelets end of ttt	Median	104	115	*0.093*
	IQR	87–130	94–129	
Bilirubin before ttt	Median	1.1	1.2	*0.982*
	IQR	0.9–1.3	0.9–1.4	
Bilirubin end of ttt	Median	1.09	1.2	*0.082*
	IQR	0.9–1.2	0.9–1.35	
Albumin before ttt	Median	3.7	3.6	*0.566*
	IQR	3.5–4.2	3.4–3.8	
Albumin end of ttt	Median	3.7	3.6	*0.256*
	IQR	3.4–4.2	3.4–3.9	
INR before ttt	Range	1–1.8	1–1.7	*0.096*
	Mean±SD	1.2±0.2	1.3±0.2	
INR end of ttt	Range	1–1.7	1–1.6	*0.078*
	Mean±SD	1.2±0.3	1.2±0.2	

Independent samples t-test for parametric quantitative data between the two groups.
Mann Whitney test for non-parametric quantitative data between the two groups.
Significant level at italics p value <0.05.
ALT, alanine transaminase; AST, aspartate transaminase; DACLA, daclatsvir; INR, international normalised ratio; LED, ledipasvir; SOF, sofosbuvir; ttt, treatment.

about 96% three patients did not achieve SVR despite the compliance to treatment, also one patient, male, 55 years old, diabetic and hypertensive stopped treatment in the last 2 weeks due to marked hyperuricaemia as the serum uric acid reached 15 mg/dL and subsequent renal affection as serum creatinine reached 4.5 mg/dL the patient was admitted to hospital and received medical treatment in the form of intravenous fluids and uric acid lowering drugs, patient improved within days and fortunately had SVR. Wyles *et al* demonstrated that the combination of

Table 5 Different variables associated with occurrence of hyperuricaemia

		Hyperuricaemia at the end of treatment		
		No	Yes	
		N=107 (83.5%)	N=21 (16.5%)	P value
Age	Range	33–69	40–66	*0.230*
	Mean±SD	51.2±7.9	53.5±8.8	
Sex	Male	56 (52.3%)	17 (81%)	***0.015****
	Female	51 (47.7%)	4 (19%)	
BMI	Range	23–33	30–36	***<0.001****
	Mean±SD	29±2.1	33.7±1.4	
Residence	Rural	52 (48.6%)	13 (61.9%)	*0.265*
	Urban	55 (51.4%)	8 (38.1%)	
Comorbidity	No	81 (75.7%)	2 (9.5%)	***<0.001****
	Yes	26 (24.3%)	19 (90.5%)	
Comorbidity	HTN	7 (6.5%)	1 (4.8%)	***<0.001****
	DM	14 (13.1%)	4 (19%)	
	HTN and DM	4 (3.7%)	6 (28.6%)	
	Gout	1 (0.9%)	8 (38.1%)	
	Free	81 (75.7%)	2 (9.5%)	
Uric acid before ttt	Range	3–7	5–7.5	***<0.001****
	Mean±SD	4.4±0.9	6.5±0.6	
Creatinine before ttt	Median	0.9	1.3	***<0.001****
	IQR	0.8–1	1.1–1.4	
Creatinine end of ttt	Median	1	1.4	***<0.001****
	IQR	0.9–1	1.4–1.9	
Bilirubin	Range	0.7–2.2	0.7–1.5	*0.076*
	Mean±SD	1.2±0.3	1.1±0.2	
Albumin	Range	3.1–4.6	3.2–4.5	*0.804*
	Mean±SD	3.7±0.4	3.7±0.3	
INR	Range	1–1.8	1–1.6	*0.571*
	Mean±SD	1.3±0.2	1.2±0.2	
Response	SVR	101 (94.4%)	21 (100%)	*0.598*
	Relapse	6 (5.6%)	0 (0%)	
Treatment	SOF LED	42 (39.3%)	9 (42.9%)	*0.758*
	SOF DACLA	65 (60.7%)	12 (57.1%)	

Independent samples t-test for parametric quantitative data between the two groups.
Mann Whitney test for non-parametric quantitative data between the two groups.
*Significant level at bold and italics p value <0.05.
BMI, body mass index; DACLA, daclatsvir; DM, diabetes mellitus; HTN, hypertension; INR, international normalised ratio; LED, ledipasvir; SOF, sofosbuvir; SVR, sustained virological response; ttt, treatment.

SOF and dacla (DCV), with once daily oral dosing, a low pill burden, good tolerability and limited drug–drug interactions, in addition to high SVR more than 90% rates.[13] El-Khayat *et al* reported that in cirrhotic patients who received sof/dacla treatment, the rates of SVR were high in both naive cirrhotic patients (94%) and 90.4% in previous treated patients, they showed that SVR rates were increased by addition of ribavirin.[14] Elnadry *et al* showed that naive cirrhotic patients child A and B who received SOF+DACLA and SOF+DACLA+ribavirin had SVR more than 97% and more than 94% in groups of patients CPT C receiving SOF+LDV and SOF+LDV+ribavirin.[15] Our results are in agreement with those of Abdel-Razek and Waked, who reported that the combination of SOF LDV in a single oral daily fixed dose resulted in an SVR in more than 93% of patients after only 8 weeks in treatment of naïve patients and more than 97% after 12 weeks of treatment.[16] In our study, adverse effects were noticed in about 39.2% in sof/ led/riba group and in 36.2% in those having sof/ dacla/riba, most adverse effects were tolerated no serious

Table 6 Logistic regression analysis for prediction of hyperuricaemia

	Simple logistic regression		Multiple logistic regression		Multiple stepwise logistic regression	
	OR (95% CI)	P value	AOR (95% CI)	P value	AOR (95% CI)	P value
Sex (male)	3.9 (1.2 to 12.3)	0.021*	44.9 (0.1 to 14 771.1)	0.198		
BMI	7.4 (3 to 18.2)	<0.001*	6.4 (1.3 to 30.5)	0.020*	5.5 (1.6 to 19.1)	0.007*
Comobidity	29.6 (6.5 to 135.7)	<0.001*	31.3 (0.2 to 361.7)	0.172		
Uric acid before ttt	21.4 (5.5 to 83.9)	<0.001*	4.6 (0.5 to 40.1)	0.163	12.1 (1.8 to 79.2)	0.010*
Creatinine before ttt	6612.4 (243.3 to 179 685.4)	<0.001*	77.7 (0 to 138 449 354)	0.553		
Creatinine after ttt	8609 (271.5 to 273 006.7)	<0.001*	8.1 (0 to 2 702 064.7)	0.747		

*Significant level at p value <0.05.
AOR, adjusted odds ratio; BMI, body mass index; NA, not applicable; ttt, treatment.

adverse effects were noticed except one patient in sof/led group developed marked hyperuricaemia and subsequent renal impairment and another one in sof/dacla group as mentioned earlier. El-Khayat *et al* showed that use of DCV plus SOF with or without ribavirin (RBV) in cirrhotics was well tolerated; patients developed mild side effects which is likely related to underlying liver disease rather to the drugs used.[14] Verna reported that available DAA regimens including sof/led and sof/dacla with or without ribavirin have marked efficacy and safety in patients with decompensated liver disease, by using this safe and effective treatment, fewer patients are being listed for transplant because of HCV-related cirrhosis.[17] In our study, we noticed hyperuricaemia in 17.6% of patients received sof/led/riba and in 15.5% of those received sof/dacla/riba, we noticed that hyperuricaemia was predominant in male sex and significantly related to higher BMI more than 30 and the presence of comorbid disease specially gout and combined diabetes and hypertension also significantly related to the level of uric acid before treatment (ttt) (more than 6.5), to the level of serum creatinine before ttt (more than 1.1) and to the level of serum creatinine after ttt (more than 1.4). By doing multiple stepwise regression analysis, it was noticed that hyperuricaemia is significantly related to the level of uric acid before ttt and BMI. A possible mechanism of hyperuricaemia is due to the increase of serum creatinine levels due to SOF and ribavirin, both of which have a potential renal toxic effect and might lead to the elevation of serum uric acid (UA) levels[18] Another possible mechanism is that SOF is a prodrug and is converted to an active metabolite (GS-461203) and is then converted to an inactive metabolite, a (GS-331007) which is a uridine analogue, this inactive metabolite can be a substrate for xanthine oxidoreductase enzyme which participates mainly in urate metabolism and production of uric acid.[19] Sato *et al* reported that elevated serum uric acid level was a remarkable side effect associated with the SOF/ribavirin regimen of ttt, they suggested that elevation of seum uric acid might be developed during this combination therapy, especially at 1st week of ttt.[18] In conclusion SOF+LDV and SOF+DACLA plus ribavirin regimens are highly effective and safe in treating chronic HCV patients with compensated liver cirrhosis hyperuricaemia is considered a potential adverse effect to direct antiviral agents containing ribavirin and may lead to serious side effects such as renal impairment especially in male patients with high BMI, elevated uric acid before treatment and in those having comorbid diseases like DM, chronic kidney disease and gout. Monitoring of serum uric acid during treatment is suggested in these groups of patients. Further studies on larger groups of patients are advised.

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