Sofosbuvir/ledipasvir safety and efficacy for HCV patients with haemodialysis and compensated cirrhosis

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Research article

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Abstract

Objectives: To evaluate the efficacy of Sofosbuvir/ledipasvir (SOF/LDV) combination for hepatitis C virus (HCV) in patients on haemodialysis and compensated liver cirrhosis as it was until recently approved by the FDA.

Design: Retrospective study on patients who were on haemodialysis and used SOF/LDV for HCV.

Setting: In one secondary health care facility (a hospital).

Interventions: Treatment consisted of 90g of SOF/ 400g of LDV once daily. Patients were assessed for HCV at end treatment after 12 weeks and after 24 weeks for patients who had compensated cirrhosis with other follow-up for symptoms assessment.

Results: The sample contained 16 males and 5 females with mean age of 40.9 years. Nineteen patients had no cirrhosis of the liver and the other two had clinical and radiological cirrhosis and had Child–Turcotte–Pugh (CTP) type B. Full follow-up was for only 20 patients and they all had HCV resolved as one patient passed away. Other factors were assessed such as HCV genotypes, but they had the same results with no difference in symptoms development (P>0.05).

Conclusion: SOF/LDV combination is suggested to be effective when the patient is on haemodialysis and had compensated cirrhosis and CTP type B without the need of dose adjustment or increase duration with no major complications in patients with HCV 1a, 1b, 4, and 5.

Strengths And Weaknesses

- Sofosbuvir/ledipasvir (SOF/LDV) regiment, a suitable substitution to the older HCV drugs, is approved for patients with HCV patients who are on dialysis by the FDA recently.
- Could not precisely determine whether the new symptoms were from the SOF/LDV or from the renal failure or other comorbidities.
- SOF/LDV was found to be effective and safe in patients on dialysis and who had compensated cirrhosis with Child–Turcotte–Pugh (CTP) type B without dose adjustment.
- Sample size, mainly for CTP B is not high to generalise the findings.
- No more severe cirrhosis was involved in the study (such as CTP C) or decompensated cirrhosis.

Background

Hepatitis C virus (HCV) infection has a prevalence of 3% worldwide and more frequent in long-term haemodialysis patients as it reached 7.5% in developed countries. Nevertheless, it was demonstrated that having a positive anti-HCV serologic was associated with a higher incidence of chronic kidney disease (CKD) in the population [1,2]. Furthermore, there was an increase of extrahepatic manifestation in CKD patients with chronic HCV such as an increase of 51% in proteinuria risk and 43% [2]. Moreover,

haemodialysis itself is a major risk for HCV despite blood testing and is one of major causes of chronic liver disease in such patients [3] and it substantially increases mortality [4]. Antiviral therapy has a positive outcome on patients on haemodialysis as it increased survival [5]. Food and Drug Administration (FDA) approved for regiments containing sofosbuvir/ledipasvir (SOF/LDV) for HCV treatment in renal disease with estimated glomerular filtration rate (eGFR) <30 and haemodialysis [6,7]. However, no much data about using this regime in decompensating liver disease is available and still not recommended [8].

Prevalence for HCV varies across the world with developing poor countries have the highest rates [9]. Syria has suffered from nine years of war and its medical sector and economy have taken a huge hit, for instance 1.5 hospital beds with only 1.22 physicians are dedicated for each 1000 of population [10]. SOF/LDV combination is now used in Syria although there is no access to many drugs due to the boycott from other countries. There are no available alternatives in Syria for patients with CKD and cirrhosis. This study contains 21 patients who used SOF/LDV regiment at Damascus Hospital although they had end-stage renal disease (ESRD), and were haemodialysis due to unavailability of other alternatives.

Methods

This study was on 21 patients who presented at Damascus Hospital for the period February 2018 and August 2019 who used SOF/LDV for HCV and had ESLD and on dialysis.

Patient and ethical consent:

This study was ethically and scientifically approved by Damascus Hospital ethical committee, and gastroenterology department which all approved according to the principles embodied in the Declaration of Helsinki. Patient written consent was taken before administration of drugs. Risks and benefits were explained and patients agreed on taken the drugs. Patients' oral consent was later taken for collecting and publishing their data for research purposes.

Inclusion/exclusion criteria:

Our sample included patients who had HCV diagnosed by polymerase chain reaction (PCR), had ESRD (GFR <15 mL/min) and were on haemodialysis when initiating HCV treatment. PCR is the best diagnostic method in haemodialysis patients [11]. We did not enrol patients who had other severe uncontrolled comorbidities that were not directly related to HCV, cirrhosis, or renal failure, such as uncontrolled diabetes with persistent high HbA1c and severe uncontrolled hypertension. We enrolled patients who used SOF/LDV for the treatment of HCV. No patient received any treatment for HCV before initiating SOF/LDV (naïve).

Child–Turcotte–Pugh (CTP) was used to determine the severity of cirrhosis. CTP is based on multiple factors, encephalopathy, ascites, bilirubin, albumin, and prothrombin time. CTP was used as it is an easy method to use in the daily practice with a high prognostic accuracy in six-month period [12].

Dosing:

Standard doses for SOF/LDV were indicated as it is suggested that no adjustment is needed for ESRD patients who are on haemodialysis which are 90 mg for ledipasvir and 400 mg for sofosbuvirfor, once daily for 12 week [6,7], except for cirrhotic patients which were treated for 24 weeks.

Progress:

Only reported newly developed symptoms were reported, or an exacerbating of symptoms after treatment initiation. Visits for new symptoms assessment and routine blood tests were conducted at the beginning, middle (six-week period) and at the end of treatment (after 12 weeks) to determine if the changes were transient or not, but they were not assessed afterwards. They were conducted on the same day according to their haemodialysis cycle (one day before haemodialysis for instance).

HCV PCR testing was conducted at the beginning, after 12 weeks (End treatment response or ETR), after ETR by 12 weeks to assess sustained virological response (SVR12) as no longer follow up was possible (SVR24). Any patient who had haemoglobin below 11 was considered as anaemia.

Statistical analysis:

Data was processed using IBM SPSS software version 25 for Windows (SPSS Inc, IL, USA). Chi-square, Fisher's exact, independent T and one-way ANNOVA tests were performed to determine the statistical significance between the Groups of cases and controls. Values of less than 0.05 for the two-tailed P values were considered statistically significant.

Results

Our sample included 16 males (76.2%) and five females (23.8%) with mean age of 40.90 ± 11.05 years. Two male patients were single (12.5%), one was engaged (6.25%), and 13 were married (81.25%) comparing to one female patient being single (20%), and four being married (80%). Ten male patients lived in the suburbs (62.5%) and six in urban area (37.5%) while all female patients lived in suburbs (Figure 1). Three males and one female patient had history of smoking with an average of 22.5 pack/year history. None of the patients was alcoholic. One had a haemorrhagic stroke in week 5 and passed away, and the remaining 20 patients continued treatment until the end, and one of them had successful renal transplant after SVR12.

All patients who were followed up until SVR12 had 0 copies of HCV RNA when using PCR when treatment started. No patient declared medication ceasing due to adverse effect or deteriorating of the symptoms. No major changes were found in liver and renal function during study period and no major complications or deaths were declared except for one patient who had the stroke and passed away in week 5.

HCV genotypes:

Ten patients (47.6%) had HCV genotype 1a, two (9.5%) genotype 1b, eight (38.1%) genotype 4, and one (4.8%) genotype 5. All females had no cirrhosis whereas three males (17.6%) had clinical and radiological findings of cirrhosis with CTP B (Figure 2). HCV genotype 1b was correlated with having headache ($P = 0.047$). Having headache was also correlated with female gender ($P = 0.026$). However, having a headache overall was only in one patient. No statistical significant difference was found when comparing HCV genotype with any of other symptoms, or smoking ($P<0.05$). HCV genotypes were also not associated with gender, and CTP scores ($P<0.05$).

CTP score and symptoms:

At the end of follow up, regardless it was full or partial, newly-developed symptoms were recorded for 17 patients containing the two patients with compensated cirrhosis and CTP B as not all data about symptoms and blood tests could be retrieved. The other 3 patients follow up for symptoms was not valid and the final patient passed away from a stroke at week 5.

Four (23.5%) patients developed lethargy or increased in tiredness, one patient (5.9%) developed sustained headache, seven (41.2%) declared an increase of nausea, five (29.4%) declared an increased frequency of passing stools, four (23.5%) an increased dizziness, one (5.9%) an increased shortness of breath, five (29.4%) an increased insomnia, eight (47.1%) an increased arthralgia, and six (35.3%) an increased mood swinging or more negative mood (Table 1).

Developing new symptoms were not statistically significantly associated with gender, or smoking, ($P<0.05$). Developing arthralgia was insignificantly correlated with smoking ($P = 0.072$). However, CTP scores were correlated with developing dizziness ($P = 0.007$) as patients with CTP B (2 patients) all had dizziness. Moreover, CTP type B was associated with shortness of breath ($P = 0.005$), and nausea ($P = 0.072$) as only one patient had shorness of breath and he had CTP type B. Although CTP B was associated with lethargy, arthralgia, and not having headaches or diarrhoea, results were insignificant ($P<0.05$). No patient developed any new pulmonary, or dermatology symptoms or coughing.

CBC and symptoms:

Mean haemoglobin level and platelet count for patients who achieved SVR12 were respectively 9.04 g/dl and 201712 x 10^9 per litter when medications were initiated and 9.95 g/dl and 205750 x 10^9 per litter after 12 weeks. Moreover, 16 patient had anaemia (Hb<11 g/dl) when initiating drugs and levels ranged from 6.3 to 12.40 g/dl). No statistical significant different was found when comparing age, haemoglobin level and platelet counts at the beginning or the end, HCV RNA copies when diagnosed, with developing lethargy, nausea, diarrhoea, dizziness, shortness of breath, insomnia, arthralgia, and mood disturbances (P<0.05). No statistical significant different was found when comparing age, haemoglobin level at the beginning or the end, HCV RNA copies when diagnosed with developing headache (P<0.05). However, it was found that having lower platelets when diagnosed or when after 12 weeks of treatment were correlated with having headache (P = 0.040 and P = 0.086 respectively).

Other variables:

No statistical significance was found when comparing HCV RNA copies, smoking cigarettes, amount smoked, haemoglobin levels, or platelet counts (P<0.05).

Discussion

Our study:

All patients who endured medications had no evidence of HCV when followed up despite having ESRD and regardless of having CTP type B or not as they had undetectable HCV RNA by PCR at SVR12. No significant side effects were developed regardless of having the clinical and radiological cirrhosis and CTP type B. No dose adjustment was required in the two patients of CTP B who had ESRD and haemodialysis and SOF/LDV was effective in these patients with genotypes of 1a, 1b, 4, and 5.

Interestingly, a slight improvement in anaemia and low platelets was noticed after HCV treatment. No correlations were found between HCV genotypes, symptoms development, HCV RNA copies when diagnosed, HCV genotypes, gender, cigarette smoking, amount smoked, and having CTP B.

Other studies:

A decline of eGFR and anaemia were observed in a large study of SOF/LDV in ESRD [7]. However, using the alternative older drugs ribavirin, interferon (IFN) alfa or pegylated IFN are associated with more severe anaemia [13]. Many adverse effects were noticed for LDV/SOF treatment, but they were mild to moderate in 93% of patients [14]. Fatigue, Headache, insomnia and nausea were the most common adverse effects [14] and anaemia has occurred in some patients [15]. Sofosbuvir is the first peg-interferon-free combination regimen with high SVR rates and has fewer side effects and requires shorter treatment compared to old

drugs [9,16]. We speculated that anaemia was alleviated as the chronic infection (HCV) was resolved and thus slightly improving the anaemia.

In decompensated liver failure, more adverse effects were found, mainly in CTP B and C. However, many studies found that most of these effects were from ribavirin [8]. Other studies also found that SVR was lower in high CTP scores with higher relapse and despite the cirrhosis they used the same fixed dose of SOF/LDV. These drugs are still not recommended in hepatic decompensation [8]. SOF/LDV is indicated in patients with HCV who did not benefit from peginterferon alfa plus ribavirin and who is treatment naïve without cirrhosis or with compensated cirrhosis [16]. In our study, regular doses were used for SOF/LDV for 12 weeks with no major side effects.

In conclusion, the results suggest that sofosbuvir/ledipasvir can be used in renal failure patients on haemodialysis to treat HCV genotypes 1a, 1b, 4 and 5, even when having clinical and radiological cirrhosis with CTP B. No dose adjustment or an increase of duration was required. Also, no more severe symptoms were developed in patients with CTP B in comparison to the other patients. Successful treatment may afterwards be associated with slight improvement of anaemia Further studies on larger study groups should be conducted to confirm these findings.

Limitations:

- No data was available on eGFR changes after giving the medications; data only contained creatinine and urea levels which were not substantially changed.
- Some patients' follow-ups for symptoms were missing.
- New symptoms could not be accurately determined if they were from medications, or other causes.
- No weekly visits were scheduled which could have left a gab in new or transient symptoms detection as visits were only scheduled on first day, six weeks, and 12 weeks after the medication and blood testing were planned to be on first day, six weeks, and12 weeks.
- The effect of other medications, medical conditions, and the aetiology of ESRD and HCV were not studied.
- Our sample study was small, particularly for CTP B patients.

Abbreviation

Child–Turcotte–Pugh	CTP
Chronic kidney disease	CKD
end-stage renal disease	ESRD
End treatment response	ETR
estimated Glomerular Filtration Rate	eGFR
Hb	haemoglobin
HCV	Hepatitis C virus
Interferon	IFN
Polymerase chain reaction	PCR
Ribonucleic acid	RNA
Sofosbuvir/ledipasvir	SOF/LDV
Sustained virological response	SVR

Declarations

- Ethics approval and consent to participate:

This study was ethically and scientifically approved by Damascus Hospital ethical committee, and gastroenterology department. Patient's written consent was taken before administration of drugs as they this drug regime was not approved at the time of treatment for dialysis patients. Risks and benefits were explained and patients agreed on taken the drugs

- Consent for publication:

Patients' oral consent was later taken for collecting and publishing their data for research purposes as it was more suitable and ethically agreed by the hospital administration.

- Availability of data and material:

Data will be made available upon reasonable request.

- Competing interests:

No competing interests to declare.

- Funding:

We received no funding.

- Author’s contribution:

BA: Conceptualisation, supervision, validation, revewing and editing the draft, project administration, and resources.

AK: Visualization, writing original draft, revewing and editing, software, data curation, methodology and formal analysis.

NH: Data curation, investigation, revewing and editing the draft, supervision, visualization, resources, and software.

RE: Investigation, methodology, project administration, resources, and visualization.

All Authors read and approved the manuscript.

- Acknowledgements:

Not applicable.

Table 1

Figures

TABLE 1
Symptoms developed in patients after 12 weeks of treatment.

Characteristic	Negative	Positive
HCV 1a (n=10)		
Lethargy	6	2
Headache	8	0
Nausea	4	4
Diarrhoea	6	2
Dizziness	6	2
Shortness of breath	7	1
Insomnia	5	3
Arthralgia	4	4
Mood disturbances	4	4
HCV 1b (n=2)		
Lethargy	1	1
Headache	1	1
Nausea	1	1
Diarrhoea	0	2
Dizziness	2	0
Shortness of breath	2	0
Insomnia	2	0
Arthralgia	1	1
Mood disturbances	2	0
HCV 4 (n=8)		
Lethargy	5	1
Headache	6	0
Nausea	4	2
Diarrhoea	5	1
Dizziness	4	2
Shortness of breath	6	0
Insomnia	4	2
Arthralgia	3	3
Mood disturbances	4	2
HCV 5 (n=1)		
Lethargy	1	0
Headache	1	0
Nausea	1	0
Diarrhoea	1	0
Dizziness	1	0
Shortness of breath	1	0
Insomnia	1	0
Arthralgia	1	0
Mood disturbances	1	0

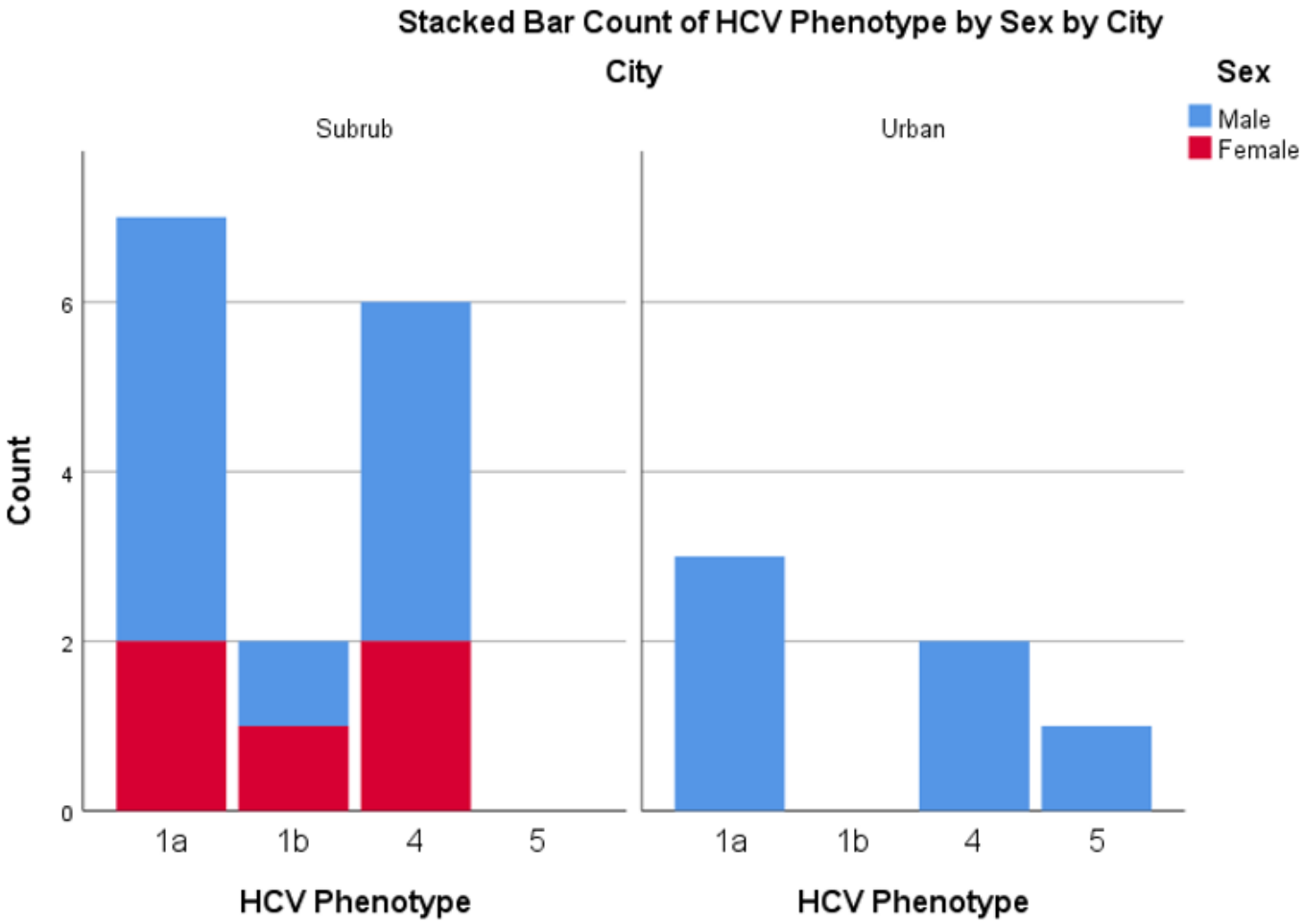

Figure 1

showing HCV genotype in urban and city according to gender.

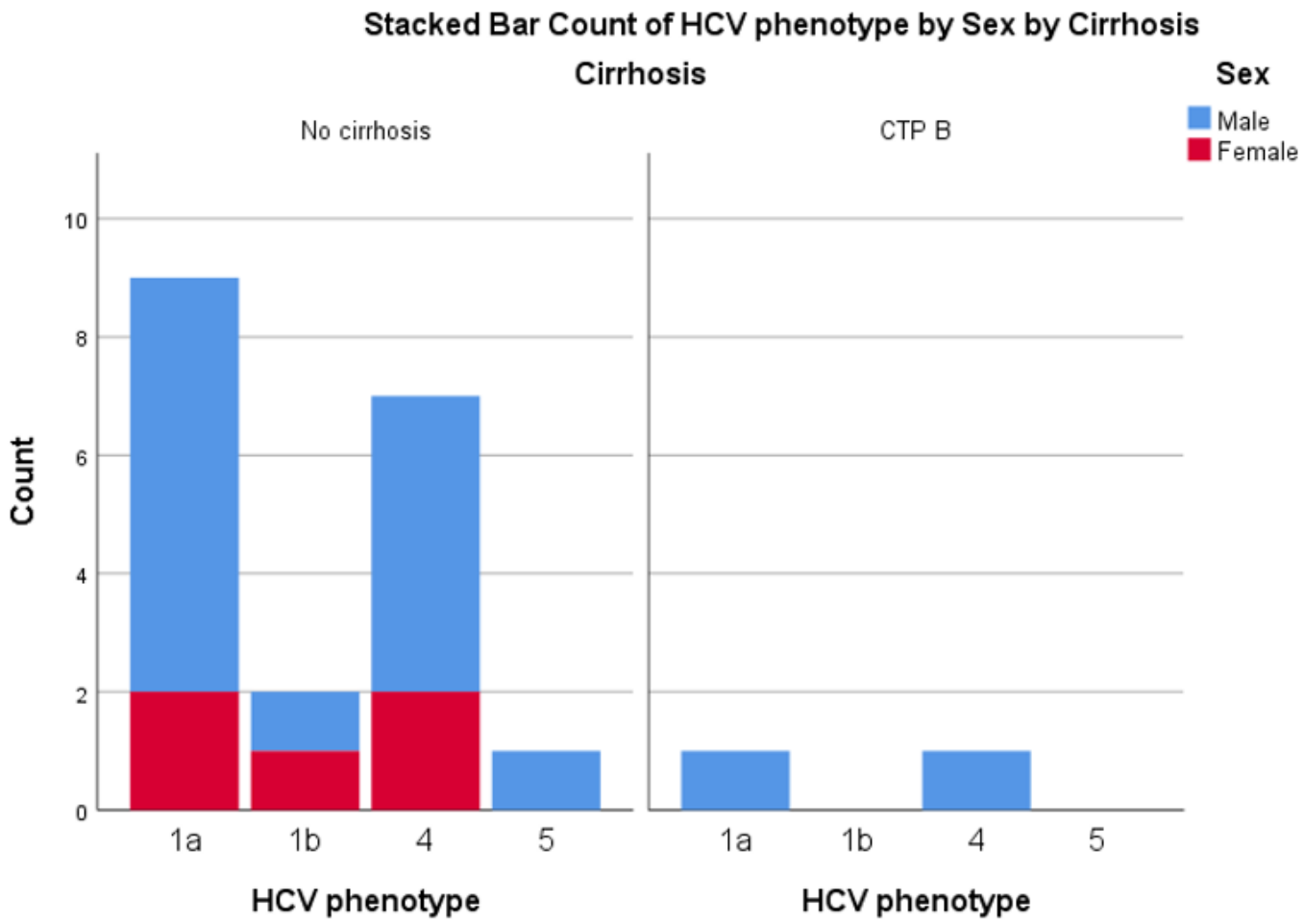

Figure 2

showing HCV genotype according to CTP, and gender.