Sofosbuvir/ledipasvir safety and efficacy for HCV patients with haemodialysis and decompensated cirrhosis: a case series

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Sofosbuvir/ledipasvir; HCV; haemodialysis; Cirrhosis; End-stage kidney disease.
Abstract
Background Sofosbuvir/ledipasvir (SOF/LDV) combination is very effective against HCV. However, it was until recently approved for use in end-stage renal disease (ESRD), and on haemodialysis. Furthermore, no much data available for SOF/LDV in compensated and decompensated cirrhosis.

Aims To assess the effectiveness and side-effects of SOF/LDV in HCV patients with ESRD, on haemodialysis, and have no cirrhosis or have either compensated or decompensated cirrhosis.

Methods Data of 21 HCV patients was collected and they were on haemodialysis and had different CTP and were assessed for HCV at end treatment after 12 weeks, and after 12 and 24 weeks of end treatment. Treatment consisted of 90g of SOF/ 400g of LDV once daily.

Results The sample contained 16 males and 5 females with mean age of 40.9 years. Three patients had decompensated cirrhosis CTP B, and four chronic hepatitis with minor cirrhotic changes with CTP A. 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.

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

Lay Summary
Sofosbuvir/ledipasvir (SOF/LDV) is approved for patients with HCV patients who are on dialysis. SOF/LDV is a suitable substitution to the older HCV drugs. SOF/LDV remained effective and safe in patients on dialysis and who had no cirrhosis or with Child-Turcotte-Pugh (CTP) of A and B compensated and decompensated cirrhosis without dose adjustment.

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. 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%. 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 and it substantially increases mortality. Antiviral therapy has a positive outcome on patients on haemodialysis as it increased survival. 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. However, no much data about using this regime in decompensating liver disease is available and still not recommended.

Prevalence for HCV varies across the world with developing poor countries have the highest rates. 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. 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), on haemodialysis and had liver cirrhosis with different levels 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. 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.

Cirrhosis:
Child–Turcotte–Pugh (CTP) was to determine the severity of cirrhosis. CTP is based on multiple factors, encephalopathy, ascites, bilirubin, albumin, and prothrombin time and the results were categorised into three groups, patients with no chronic hepatitis, chronic hepatitis with minor cirrhotic features CTP A, and decompensated cirrhosis CTP B. CTP was used as it is an easy method to use in the daily
practice with a high prognostic accuracy in six-month period. Decompenated cirrhosis was defined as experiencing encephalopathy, fluid overload or variceal haemorrhage that was resolved within six months before treatment.

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. 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).

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 sofosbuvir, once daily for 12 week.

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 and 24 weeks to assess sustained virological response (SVR12 and SVR24, respectively). 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 (Fig. 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 with CTP A had successful renal transplant after SVR24.

All patients who were followed up until SVR24 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. ALL patients with CTP B had decompensated cirrhosis as two of them had fluid overload with ascites and one had encephalopathy in the last six months.

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 or chronic hepatitis whereas ten males (58.8%) had no cirrhosis or chronic hepatitis, four (23.5) had chronic hepatitis with CTP A, and three (17.6%) had decompensated cirrhosis with CTP B (Fig. 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, being from suburbs, marital status, 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 two patients with CTP B, four with CTP A 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).

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

Developing new symptoms were not statistically significantly associated with gender, smoking, marital status, or being from urban or rural area (P < 0.05). Developing arthralgia was insignificantly correlated with smoking (P = 0.072). However, CTP scores were correlated with developing dizziness.
(P = 0.020) as CTP A had more dizziness than patients with no cirrhosis or chronic hepatitis and patients with CTP B (2 patients) all had dizziness. Moreover, shortness of breath was associated with CTP B (P = 0.019). Although CTP B was associated with lethargy, nausea, 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 SVR24 were respectively 9.04 g/dl and \(201712 \times 10^9\) per litter when medications were initiated and 9.95 g/dl and \(205750 \times 10^9\) 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:**
Gender, being married, or being from suburbs were not significantly associated with HCV RNA copies, amount smoked, haemoglobin levels, or platelet counts (P < 0.05). Higher CTP scores was associated with living in urban areas but P = 0.059 and when comparing having CTP A or B with not, living in urban areas was correlated with having chronic hepatitis or cirrhosis (P = 0.040). CTP scores were not associated with age, HCV RNA copies, 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 CTP scores as they had undetectable HCV RNA by PCR until SVR24 and no significant side effects.
were developed regardless of having decompensated cirrhosis or not. No dose adjustment was required in CTP A, and CTP B in patients with ESRD and haemodialysis and SOF/LDV was effective in these patients with genotypes of 1a, 1b, 4, and 5, even in cases of decompensated cirrhosis. 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, marital status, cigarette smoking, amount smoked, living in urban areas, age, and cirrhosis. Higher haemoglobin and lower HCV copies were associated with being married. More severe cirrhosis and developing shortness of breath were insignificantly correlated with living in urban areas. Living in urban areas was also correlated with worse cirrhosis or chronic hepatitis. Only one patient had headache and thus the results relating to it are unreliable.

Other Studies:
A decline of eGFR and anaemia were observed in a large study of SOF/LDV in ESRD. However, using the alternative older drugs ribavirin, interferon (IFN) alfa or pegylated IFN are associated with more severe anaemia. Many adverse effects were noticed for LDV/SOF treatment, but they were mild to moderate in 93% of patients. Fatigue, Headache, insomnia and nausea were the most common adverse effects and anaemia has occurred in some patients. 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. 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, most of these effects were from ribavirin. SVR was also 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. 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. 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 decompensated cirrhosis or with CTP A, or B. No dose adjustment or increase of duration was required. Also, no more severe symptoms were developed in patients with cirrhosis in comparison to not having cirrhosis. Successful treatment may afterwards be associated with slight improvement of anaemia and living in urban areas was correlated with having higher CTP scores. 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 gap 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, 12 weeks, and 24 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 A and B.

Abbreviations

| Abbreviation                      | Description                     |
|----------------------------------|---------------------------------|
| 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.

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Author’s contribution:
BA: Conceptualisation, supervision, validation, reviewing and editing the draft, project administration, and resources.

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

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

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

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**Figures**
Figure 1

showing HCV genotype in urban and city according to gender.
Figure 2

showing HCV genotype according to CTP, and gender.