Treatment with Sofosbovir+Daclatasvir in HIV/HCV Co-Infected Patients: A Real-World Perspective

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ABSTRACT

Determining the effect of new antiviral (Direct-Acting Antivirals; DAAs) medicines, such as SOF + DCV on HCV treatment in HIV/HCV co-infected patients. HIV/HCV co-infected patients were treated with SOF + DCV combination for 12 weeks and the drug dosage was adjusted according to ART in case needed. APRI, FIB4 Index and MELD Score formulas were used to examine the effect of treatment on the degree of liver fibrosis and HCV RNA PCR was performed to evaluate the response to 12-week treatment after the completion of the treatment. Twenty-four male patients with the mean age of 44±7.73 years were enrolled in the study with 58.3% having a history of unprotected sexual contact and 100% having a history of injectable drug use. The mean HCV viral load at the baseline was 6.3Log_{10} IU/ML and 5 cases having undetectable viral load were excluded. Seven patients had GT1, 6 patients had GT3 and other cases were not detectable. HCV RNA PCR was undetectable in 18 patients 12 weeks after the treatment. Moreover, the decrease in ALT and AST (P= 0.001), the increase in platelet count (P= 0.016), and the increase in cr (P= 0.032) were significant, which partially justified the reduction in liver fibrosis using non-invasive methods. Twelve weeks after treatment, 19 patients were tested for HCV RNA PCR, the HCV viral load was not detectable in 18 patients and reached to SVR12 (sustained virologic response) rate 94.7%. According to the current study, treatment with SOF + DCV combination was associated with SVR12 rate 94.7%. Thus, SOF + DCV combination can now be used as an effective medicine in the treatment of all hepatitis C genotypes in HIV/HCV co-infected patients.

Key Words: *SVR12, Sofosbuvir, Daclatasvir, HIV, HCV*

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INTRODUCTION

According to the World Health Organization (WHO) estimates, about 35 million people in the world are currently infected with the human immunodeficiency virus (HIV) [1]. Nearly 170 million people suffer from hepatitis C, of whom 2.3 to 5 million are HIV/HCV co-infected [2]. It is estimated that 0.3% of these have chronic hepatitis C in Iran, 11% of whom are HIV/HCV co-infected [3].

The largest affected population is injectable drug users [4]. Concomitant HIV infection may lead to the acceleration in the complications of chronic hepatitis C like progression towards decompensated liver cirrhosis and the emergence of hepatocellular carcinoma [5]. Increased HCV RNA levels in patients with HIV infection are 8 times faster and HCV RNA levels are inversely correlated with CD4 count [6].

The new generation of DAAs is effective in both groups of patients - with HCV infection alone and HIV/HCV co-infected - given the availability of their oral form, better tolerance, lack of need for interferon and proper virologic response [7]. Sofosbuvir (NS5B polymerase inhibitor) and daclatasvir (NS5A inhibitor) - once a day orally - are both effective in all genotypes with minimal drug interactions with ART drugs [8]. In Iran, the focus of health care has been mostly on HIV and concomitant diseases like HCV have been neglected, whose results in the near future would be irreversible liver cirrhosis, the

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continuation of hepatocellular carcinoma, and HCV transmission in the community if not diagnosed, particularly by injectable drug use [9].

Objectives

Determining the effect of new antiviral (DAAs) medicines, such as SOF + DCV on HCV treatment in HIV/HCV co-infected patients.

MATERIALS AND METHODS

This study was conducted in Mashhad Counseling center of Infectious-Behavioral Diseases Reference Center. The total number of HIV/HCV co-infected patients was 60 based on available data. 26 patients were selected with informed consent based on the adherence to HIV treatment, regular referrals to the health center, and more probability of pursuing HCV treatment. Exclusion criteria were the lack of satisfaction and proper compliance or lack of adherence to the treatment. One patient passed away at the beginning of the study and one case was excluded because of unwillingness to follow-up.

Design of the Study

GeneXpert PCR was done for 24 patients to detect HCV viral load and to determine genotype. HIV viral load, CD4 and HBsAg levels were measured for the patients and other demographic information was extracted from patient records. Basic laboratory tests like liver enzyme levels, INR, Alb, platelet, Cr and αFP were requested. A liver ultrasound was done to evaluate the liver status. Then SOF + DCV combination was administered and the drugs` doses were adjusted according to ART regimen. The patients were treated for 12 weeks and periodic visits were performed to evaluate the adherence to the treatment. Twelve weeks after the completion of treatment, HCV viral levels were evaluated using TaqMan Real Time PCR method.

Examination of liver fibrosis

To evaluate liver function status, non-invasive methods such as AST to PLT index (ARPI) were used:

$$\text{APRI} = \frac{\text{AST level}/(\text{AST}/\text{ULN})}{\text{platelet count} \times 109/\text{L}} \quad (1)$$

Formula FIB-4:

$$\text{Fib} - 4\ \text{score} = \frac{(\text{age[years]} \times \text{AST[IU/L]})}{\text{plateletcoun}\sqrt{ALT\,[\text{IU/L}]}} \quad (2)$$

[10]

Moreover, MELD score [5] was used and data was analyzed using SPSS 16.

RESULTS AND DISCUSSION

This cross-sectional and prospective study was conducted in 2018-2019 on 24 male patients with the mean age of 44±7.73 years. Based on the analyses, 66.7% were married and 87.5% had no university educations.

Additionally, 58.3% had a history of unprotected sex with 100% having a history of injectable drug use.

Throughout the study, for the possible causes of liver involvement that ended in advanced liver disease, 79.2% had a history of alcohol use. None of the patients was HBs Ag positive and none had previous treatments for HCV.

The patients were divided into two groups <50 IU / ML and≥ 50 IU / ML based on HIV viral load and <200 cell / mm^3 and≥ 200 cell / mm^3 based on CD4. All the patients were being treated with ART regime. Two patients had an increase in the levels of bilirubin up to about 2 mg / dl. Primary HCV RNA PCR was not diagnosable in 5 patients who were excluded from the study.

Eighteen patients had APRI less than 2 and one case had APRI more than 2. Moreover, 19 patients had FIB4 less than 3.25 and all patients had MELD score less than 18.

Nineteen patients underwent SOF + DCV regimen for 12 weeks and quantitative HCV RNA PCR was performed again 12 weeks after the treatment. In 18 cases, the viral level was not detectable and reached SVR12 rate 94.7%, one case had a detectable viral level of 5Log 10 IU / ML **(Table 1)**.

Table 1. Demographic information and disease characteristics

Parameter	N (%)
Male	24(100%)
IDU	24(100%)
Mean Cr(mg/dl)	0.93±0.1
Mean Plt(×10^3/µl)	172±5.18
Mean AST(u/l)	59.73±6.75
Mean ALT(u/l)	62±4.43
HCV disease characteristics	
GT1	7(36.8%)
GT2	6(31.57%)
Unknown	6(31.57%)
HCV RNA, mean range, log_{10}IU/ML	6.3
HIV-1 disease characteristics	
HIV-1 RNA<50 copies/ml	16(66.66%)
HIV-1 RNA≥50 copies/ml	8(33.33%)

Mean CD4 cells/mm^3	411.82±253.82
CD4<200	4(66.66%)
CD4≥200	20(83.33%)
HIV-1 treatment *	
NNRTI	18
PI	3
INSTI	3

* Some patients received ART regimens with three different drug groups.

Decrease in the liver enzyme level (P= 0.001), increase in the platelet count (P= 0.016) and increase in serum Cr (P= 0.032) were observed that were statistically significant **(Table 2)**.

Table 2. Parameters modified with the treatment

Median AST	19	P-value 0.001
Median ALT	19	P-value 0.001
Mean Plt	211050±45765	P-value 0.016
Mean Cr	1±0.17	P-value 0.032

Although ART did not directly inhibit HCV replication, it reduced the progression of liver disease by reducing HIV replication and increasing CD4 levels. Thus, HCV Ab testing was initially examined in all HIV patients [11].

In this study, 24 HIV / HCV co-infected patients, who were all being treated with ART, were selected.

As SOF + DCV combination is available in the Iranian market and is effective on all genotypes and limited interactions with ART regimens [12], despite Guideline EASL 2018 that excluded this compound, and while being recommended by American Guidelines[1], this was designed to examine the response to the treatment with this combination [13].

The standard DCV level was 60 mg daily, which was reduced to 30 mg daily in combination with ART diet containing PI, and increased to 90 mg daily in combination with EFV and other NNRTIs [14].

The patients were treated with sof + dcv regimen for 12 weeks and the response to the treatment was evaluated 12 weeks after the treatment with HCV RNA PCR, where the virus level was not detectable in 18 patients and in only one case of 5Log$_{10}$ IU / ML viral count was reported. Furthermore, 94.7% of the patients reached SVR12.

Similar studies have been done on HIV/HCV co-infected patients with the same drug combination, which were in line with the results of the present study. For instance, in the studies by DLWyles, Anne F. Luetkemeyer, Jurgen K Rockstroh, M. Mandrofer, Stephan D. Shafran, SVR12 rates were 97%, 95%, 92%, 100% and 100%, respectively [1, 12, 15-17].

Only a few studies of HBV co-infection had been studied, including the study by Jurgen K Rockstroh, where three patients had co-infection with HBV-HCV-HIV and the ART regimen of all three patients included tenofovir and ametriclibine, which also affected HBV [16].

All patients with HIV / HCV co-infection should be screened for HBV, since HBV activation may occur during the treatment of HCV with DAAs. The patients with active HBV infection should switch to ART prior to or at the beginning of HCV treatment, such as two HBV-effective drugs [14]. In our study, all patients had negative HBS Ag test.

In the present study, a decrease in liver enzyme levels (P= 0.001) and an increase in platelet count (P= 0.016) were observed, which had significant changes. In this study, FIB4T, APRI and MELD Score formulas were used to evaluate liver dysfunction and fibrosis. APRI of a patient was above 2 with a decrease in platelet count and AST decrease of less than 2. Other parameters were within normal range before the treatment. In the studies with similar design to that of the present study, less attention has been paid to the effects of treatment response on the process of hepatic enzymes depletion, platelet elevation, and thus the effect on hepatic fibrosis improvement.

In the present study, two cases of elevated bilirubin levels before the treatment with hepatic enzymes near normal were observed, which could be due to the effect of ATZ on bilirubin levels [18].

In this study, the mean cr before the treatment was 0.94 and it was 1 after the treatment, with a significant increase in creatinine (P= 0.032), which could be due to the side effects of DAAs, HIV progression (P= 0.032) or interfering with other drugs, including the effects of TDF on renal function [19]. Similar studies have focused less on this treatment`s side effects.

As the response rate to the treatment with DAAs was high, pre-treatment of drug resistance testing is not suggested [20].

Anne F. Luetkemeyer and D.L.Wyles have shown DCV resistance as the causes of virologic failure [12, 15].

Similar to HIV / HCV co-infection, diabetes can exacerbate the consequences of HCV in patients with HCV-like HIV infection [1].

In the present study, for the patients with no response to the treatment, adherence to the treatment, re-infection with HCV after the completion of the treatment, or increased viral burden of HIV under the treatment (failure of HIV treatment) and other underlying diseases including diabetes and reactivation of HBV virus, despite HBs Ag negative and or suffering from it should be considered.

[1]patient with hiv/hcv coinfection [Internet]. Available from: www.hcvguidence.org.

Among the limitations of the study, one can cite to the inefficiency of patients, poor socioeconomic status, lack of funding, and lack of access to other DAAs.

According to our study, SOF + DCV combined therapy could be used as an effective drug on all genotypes for the treatment of hepatitis C in HIV/HCV co-infected patients.

CONCLUSION

According to the current study, treatment with SOF + DCV combination was associated with 94.7% SVR12. Thus, SOF + DCV combination can now be used as an effective medicine in the treatment of all hepatitis C genotypes in HIV/HCV co-infected patients.

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