Does Ledipasvir-Sofosbuvir Teatment Prevent Hepatocellular Cancer in Hepatitis C Patients? Single Center Real Life Data

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ABSTRACT

Backgraund/Aims: *We aimed to evaluate treated with ledipasvir-sofosbuvir ± ribavirin in noncirrhotic and cirrhotic patients due to hepatitis C and to detect hepatocellular cancer (HCC) frequency in these patients.*

Materials and Methods: *The characteristics and treatment outcomes of the patients were evaluated. Patients treated with ledipasvir-sofosbuvir ± ribavirin 3 or 6 months. The patients were followed by monthly outpatient controls, during theraphy, than once in 3 months.*

Results : *Of the total 35 patients, 18 (52%) were male and mean age was 63.2 ± 11.9 (range 22-86) years. 22 of the patients (63%) were cirrhotic. 27 (77%) patients were over 60 years old. 34 patients (97%) were genotype 1-1a-1b, and 1 genotype 4. In two patient, HCC was detected, second month of treatment and 2 months after the end of treatment.*

Conclusion: *Our HCV patients are mostly genotype I, cirrhotic, two of third elderly, two of third treatment experienced. Three patients died due to HCC, hepatic failure and CRF, and two patients had HCC during and after treatment. Ledipasvir-sofosuvir ± ribavirin therapy of chronic hepatitis C does not alter the short-term risk for HCC in patients with liver cirrhosis.*

Keywords: *HCV, ledispasvir-sofosbuvir, ribavirin, HCC*

INTRODUCTION

The frequency of hepatitis C virus (HCV) in our country is around 1% (1).HCV can lead to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). Chronic hepatitis C is the leading cause of end-stage liver disease, HCC and liver related death. In cirrhotic patients there is a 1-5% annual risk of HCC and a 3-6% annual risk of hepatic decompensation. In decompensated cirrhotic patients the risk of death in a year is 15-20 %. Eradication of HCV with antiviral therapy reduces the risk of HCC in patients with chronic hepatitis C, but the risk is not eliminated (2).

Direct-acting antivirals (DAAs) have become widely used for patients with HCV decompensated cirrhosis. New DAAs cure HCV infection in over 90% of patients. Virological responses and early improvements in liver function are excellent, but the longer term impact of viral clearance on end-stage liver disease complications is unclear (3, 4).

HCC represents a serious complication of HCV-related cirrhosis. Sustained virological response (SVR) following interferon-based antiviral treatment of chronic hepatitis C is associated with decreased long-term risk of complication and HCC. An unexpected high rate of HCC recurrence following antiviral treatment using DAAs has recently been reported (5, 6). Other hand in some studies there is no evidence for differential HCC occurence or recurrence risk following SVR from DAAs and IFN-based therapy (7).In an open-label, randomised, phase 2 trial suggest that the fixed-dose combination of sofosbuvir-ledipasvir alone or with ribavirin has the potential to cure most patients with genotype 1 (8).In this study, it was aimed to evaluate treated with ledipasvir-sofosbuvir ± ribavirin in noncirrhotic and cirrhotic patients due to hepatitis C and to detect hepatocellular cancer (HCC) frequency in these patients.

MATERIALS AND METHODS

Patients were divided into 2 groups; ledipasvir 90 mg-sofosbuvir 400 mg single fixed-dose for 6 months (group 1) and ledipasvir 90 mg-sofosbuvir 400 mg + ribavirin 200 mg for 3 months (group 2).The characteristics of patients,

endications, treatment side effects and treatment outcomes of patients were evaluated, between October 2016 and Agust 2018. The patient's monthly policlinic controls were performed. End of the first month, end of the treatment, and 3 month after, end of treatment HCV RNA evaluated.

RESULTS

Of the total 35 patients, 18 (52%) were male and mean age was 63.2 ± 11.9 (range 22-86) years. 22 of the patients (63%) were cirrhotic. 27 patients (77%) were over 60 years old. 34 patients (97%) were genotype 1-1a-1b, and 1 genotype 4. 3 patients (8.5%) were HCV relapse after tarnsplantation.

Group 1 had 17 patients (48%), 9 men (53%) and a mean age was 64 ± 14.3 (range 22-86), 15 were cirrhotic (88%). 9 patients were genotype 1, 6 genotype 1b, 1 genotype 1a, 1 genotype 4. Treatment indications were cirrhosis 10 patients (59%), recurrence with / without cirrhosis 5 patients, cirrhosis and chronic renal failure (CRF) 1 patient and in post transplantation recurrance 1 patient. 16 of these patients (95%) achieved rapidly virologic response (RVR), 1 patient was HCV-RNA positive end of first month. End of virological response (EVR) in 14/14 patients, and 12 week after treatment, sustained virological response (SVR12) in 10/10 patient. One patient died of complications of CRF, 1 elderly decompansated cirrhotic patient hepatic failure and 1 patient died of advanced HCC during the follow-up.

Group 2 had 18 patients (52%), 9 were male (50%) and the mean age was 62.3 ± 9.1 (range 35-73). 11 patients were genotype 1, 6 genotype 1b, 1 genotype 1a. Treatment indications in these patients were cirrhosis in 4 patients, recurrence with or without cirrhosis11, recurrence after transplantation in 2 patients, and CRF in 1 patient. 3 patiens was hepatitis B virus (HBV) co-infected. In group 2, RVR, EVR and SVR12 were obtained in all 18 patients. In two patient, HCC was detected, second month of treatment and 2 months after the end of treatment. 3 of patients with HCV infection who were co-infected with HBV achived SVR with the combination of ledipasvir-sofosbuvir + ribavirin for 12 weeks. In two recurrent HCV infection after liver transplantation patients ledipasvir-sofosbuvir + ribavirin therapy is an effective (achived SVR 12) and well-tolerated. But HBV reactivation was seen HBsAg-negative recurrent HCV infection after liver transplantation during second month of therhapy, and tenofovir disoproxil treatment started.Patient follow-up and treatment were continuing.

DISCUSSION

With the approval of DAAs in 2011 and anticipation of interferon (IFN)-free regimens, HCV chronically infected patients were treated more effectively (9). DAAs regimens for the treatment of HCV has led to the expansion of therapy to include patients with cirrhosis (10). In our series of the total 35 patients, 22 of the patients (63%) were cirrhotic.

In a large cohort study, Maan R et al. showed that anti-HCV therapy was safe and effective in patients with compensated (Child-Pugh (CP) score of A) cirrhosis. They accepted that the patients with decompensated (CP score of B/C) cirrhosis, albumin level less than 3.5 g/dL, MELD score of 14 or greater, and the presence of HCV genotype 3 were important risk factors for hepatic decompensation during DAA-based treatment (11). In our study, we showed that ledipasvir-sofosbuvir ± ribavirin therhapy was safe and effective in both compansated and decompansated patients. There was no patient with genotype 3 in our series.

Real-world setting, the treatment of chronic HCV genotype 1 resulted in a high rate of SVR, especially in patients without cirrhosis (12). In our patients, the first treatment results were successful in both groups. In ledipasvir-sofosbuvir group EVR was in 14/14 patients, SVR12 in 10/10 patient, in ledipasvir-sofosuvir + ribavirin group EVR and SVR were obtained all patients.

In an open-label, randomised, phase 2 trial suggest that the fixed-dose combination of sofosbuvir-ledipasvir alone or with ribavirin has the potential to cure most patients with genotype 1 HCV, irrespective of treatment history or the presence of compensated cirrhosis (8). We demonstrated that there was no differences in SVRs between two groups.

A careful baseline evaluation and a strict monitoring allow to optimise management and outcome of DAAs in old patients (13). In our elderly patients well tolerated therhapy and their therhapy results were exellent. Only a decompansated cirrhotic man (68 years old) died due to hepatic failure.

In a prospective study, the combination of ledipasvir-sofosbuvir for 12 weeks produced

an SVR in 100% of patients with HCV infection who were co-infected with HBV (14). Our co-infected three patients achived SVR with the combination of ledipasvir-sofosbuvir + ribavirin for 12 weeks.

Co-infection with HBV does not have a negative impact on the efficacy of anti-HCV treatment, but HBV-DNA should be monitored to overcome the risk of HBV exacerbation (15). HBV reactivation was rare in HBsAg-negative patients treated with DAA therapy (16). In our series a HBsAg-negative recurrent HCV infection after liver transplantation patients was seen HBV reactivation during second month with the combination of ledipasvir-sofosbuvir + ribavirin theraphy, and tenofovir disoproxil treatment started.Ledipasvir-sofosbuvir with and without ribavirin therapy is an effective and well-tolerated interferon-free treatment for recurrent HCV infection after liver transplantation (17, 18). In our group 2, two recurrent HCV infection after liver transplantation patients achived SVR with the combination of ledipasvir-sofosbuvir + ribavirin for 12 weeks and in group 1, 1 patient achived SVR with single dose, 6 month.

Since DAAs for treatment of HCV were introduced, conflicting data emerged about the risk of HCC after IFN-free treatments (19). Recent studies have reported higher rates of HCC in individuals treated with DAAs. However, making definitive conclusions has been challenging due to the heterogeneous populations and methodologies of these reports (20). The risk for early HCC occurance and recurrence following viral eradication by IFN-free DAAs therapy may be similar to that in IFN-based therapy (21-23). Ioannou GN et al reported DAA-induced SVR is associated with a 71% reduction in HCC risk. Treatment with DAAs is not associated with increased HCC risk compared with treatment with IFN (24). HCC recurrence rate was significantly lower among patients treated with DAAs compared with untreated patients. However, in patients with SVR, the absolute risk of HCC remained high in patients with established cirrhosis (25, 26). In ours series 3 patients had HCC. 1 patient had initial HCC, she died during treatment in the group 1. 1 patient detected HCC first month of theraphy and 1 patient detected HCC after second end of treatment in group 2. All HCC patients had decompaseted cirrhosis. We thought ledipasvir-sofosuvir ± ribavirin therapy of chronic hepatitis C does not alter the short-term risk for HCC in patients with liver cirrhosis.

In a study amongst 317/406 patients who achieved SVR at 24weeks post-treatment, there were 9 deaths (3%), 17 new liver cancers (5%), 39 transplantations (12%) and 52 with serious decompensations (16%), over 15 months (27). In our series three patients (8.5%) died (1 hepatic failure, 1 CRF, 1 HCC), 3 patients (8.5%) had HCC (1 patient it was known HCC, 1 patient during, 1 patient two month after end of treaatment).

In conclusion, our HCV patients are mostly genotype I, mostly cirrhotic, two of third of the patients are elderly, two of third treatment experienced. Three the patients were died due to HCC, hepatic failure and CRF, and two patients had HCC during and after treatment. In the other patients, the first treatment results were successful in both groups. We concluded that ledipasvir-sofosuvir ± ribavirin therapy of chronic hepatitis C does not alter the short-term risk for HCC in patients with liver cirrhosis. All cirrhotic patients should be closely monitored and followed during and after antiviral therapy.

Table: *characteristics and treatment outcomes of the patients*

	Group 1	Group 2	Total	p
Number/sex	17/9 M	18/9 M	35/18 M	p>0.5
Mean age	64 ± 14.3 (22-86)	62.3 ± 9.1 (35-73)	63.2 ± 11.9 (22-86)	p>0.5
Cirrhosis	15 (88%)	7 (40%)	22 (63%)	P<0.005
Post-tx recurrance	1	2	3	
RVR	16/17	18/18	34/35	p>0.5
EVR	14/14	18/18		p>0.5
SVR12	10/10	18/18		p>0.5
HCC	1	2	3	
Died	3		3	P<0.005
Treated HBV co-infection		3	3	P<0.005

M: male, post-tx: post transplantation, RVR: rapidly virological response, EVR: end of treatment response, SVR12: 12 th week of sustained virologival response, HCC: hepatocellular carcinom, HBV: hepatiris B virüs.

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