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Treatment of Chronic HCV Infection with Direct Acting Antivirals

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Objectives: This study was conducted to discover the treatment outcome and side effects of chronic hepatitis C virus patients treated with Direct-Acting Antivirals (DAAs). **Methods:** Based on the Liver Center database, we studied the treatment effect of Sofosbuvir 400 mg/Ledipasvir 90 mg in 1109 patients with chronic hepatitis C virus infection during the time period from December 2015 to December, 2018. **Results:** In patients treated with Sofosbuvir/Ledipasvir, the sustained viral load (SVR12) was 97.9% (1086/1109) 12 weeks after the treatment. The SVR12 was 99.2% (845/851) in HCV-infected non-cirrhotic patients, 93.4% (241/258) in patients with cirrhosis, and 80% (8/10) among patients treated for liver cancer. The SVR12 (19/25) was lowered to 76% at 12 weeks of treatment with Sofosbuvir 400 mg/Daclatasvir 60 mg in DAA-failure patients 23/1109 (2.07%). **Conclusions:** SVR12 rates in non-cirrhotic and cirrhotic patients were 99.2% and 93.4%, respectively, while it was 80% in liver cancer patients after DAA treatment. As for patients with viral relapse, 76% of them were successfully retreated with second-line DAA treatment. During the DAA treatment, only 17.6% of all patients had some adverse effects related to DAA treatment, thus, DAA treatment is suitable for Mongolian patients and has less adverse effects.

Keywords: Direct-Acting Antivirals, Hepatitis C, Ledipasvir, Sofosbuvir

Introduction

Hepatitis C is a disease with a significant global impact. Hepatitis C virus (HCV) is a major cause of progressive liver disease with an estimated 185 million people infected worldwide, 350,000 of whom die each year due to this chronic infection and its complications. HCV infection leads to chronic infection in up to 80% of infected individuals. The main complications of HCV are severe liver fibrosis and cirrhosis, and 30–50% of individuals with cirrhosis go on to develop hepatocellular carcinoma [1, 2].

In the last few years, numerous directly acting antiviral agents (DAAs) have been implemented successfully in treatment

algorithms of HCV infection. Initially, as combination therapy of pegylated interferon (PEG-IFN) α with ribavirin, and more recently and most importantly, as PEG-IFN-free combination therapies, DAA-based regimens result in HCV eradication in the vast majority of patients with chronic hepatitis C. [3] The prevalence of HCV has already peaked or is starting to decline in some countries due to the implementation of blood-donor screening and effective treatment, however, globally, HCV-related complications such as cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC) are expected to increase in several countries over the course of the next decade with today's treatment paradigm [4].

Quantitative HCV RNA measurement at baseline in antiviral therapy is crucial to determine treatment duration. Traditionally, it has been repeated 24 weeks after treatment completion to assure that a sustained virologic response (SVR) has been achieved. However, as the probability of virologic relapse is similar after 12 and 24 weeks, the new time point for assessment of final virologic treatment outcome is 12 weeks after the end-of-treatment [5]. The goal of antiviral therapy is to cure hepatitis C via a sustained elimination of the virus. A sustained elimination of HCV is achieved if the HCV RNA remains negative three to six months after the end of treatment (sustained virologic response, SVR-12 or SVR-24). Follow-up studies documented that more than 99% of patients who achieved a negative SVR-24 after interferon alfa (IFN) based therapies remain HCV RNA negative 4-5 years after the end of treatment and have no signs of hepatitis documented [6, 7].

Sofosbuvir is a nucleoside analogue molecule, which has NS5B inhibitor which is strongly effective against all HCV genotypes. It has a very high genetic and fitness barrier to the development of resistance. Sofosbuvir (SOF) (Sovaldi®) was the first available once-daily NS5B polymerase inhibitor (approved 12/2013 by FDA and 1/2014 by EMA). The first long-term follow-up studies after therapy with DAA confirm the durability of SVR-12 in more than 99% of treated patients [8].

The combination of SOF with the NS5A inhibitor ledipasvir (LDV) was the first NS5A based IFN free combination therapies that has also shown >90% SVR [9-12]. Importantly, the combination SOF/LDV (Harvoni® approved in 10/2014 by FDA and 11/2014 by EMA) showed >95% SVR in genotype 1(GT1) patients with treatment failure on PEG - IFN + RBV/ PI triple therapies [9, 11]. In a phase 3 pivotal study, the overall SVR rates were 99% in treatment-naïve patients who received 12 weeks of SOF/LDV [11].

The combination of SOF and LDV is available as a single-tablet fixed-dose combination (Harvoni®, Gilead Sciences). The single pill contains the NS5B polymerase inhibitor SOF (400 mg) and the NS5A inhibitor LDV (90 mg). SOF/LDV is recommended for patients infected with genotype 1, 4-6. Some data (phase 2 and real-world) are available for genotype 3 (GT3) patients [13], but as better treatment options for GT3 are available, SOF/LDV is not recommended for GT3 [14].

The incidence of HCC in Mongolia is 11 times higher than the world average and is mostly caused by hepatitis B, C and D viruses. The incidence of liver cancer in Mongolia is 8 times higher than the world average amongst women and 16 times higher among men. According to the National Cancer Center Disease (NCCD) report 2016, HCV infection is the major cause of HCC as a public health problem. Mongolia is one of the countries that has a high prevalence of HCV, and its related liver disease. According to the NCCD report of 2016, it was estimated that 121.3 per 100 000 men and 87.9 per 100 000 women were diagnosed with HCC [15]. The main reasons for liver cirrhosis and HCC are considered to be chronic viral hepatitis [16]. According to the studies, the prevalence of HCV in Mongolia is around 10-15%, which makes Mongolia a high incidence country for HCV infection [16, 17], in addition, the 1b genotype is dominating with 98% among HCV patients [16]. Correspondingly, the aggressive status of HCV and treatment outcome varied from the dominant genotype of HCV infection in Mongolia when only IFN contained regimens were available [15].

Until 2013, HCV treatment was very complicated, luckily, since 2015, DAA treatment brought a great chance of recovery to the world. Therefore, Mongolia was encouraged by receiving DAA drugs for HCV patients. However, the treatment result of DAA drugs has not been studied yet in Mongolia. Thus, we aimed to evaluate treatment results and side effects in both treatment-naïve and DAA failure patients during DAA treatment.

Materials and Methods

Based on the Liver Center database, we retrospectively studied 1109 patients with chronic HCV infection for their DAA treatment effect during the time period from December 2015 to December 2018. The study was planned with 2 phases on the same samples

patients: the 1st phase was the treatment period and the 2nd was the period to estimate SVR12, and adverse effects.

In order to evaluate the patient's status, AST to Platelet Ratio Index (APRI) score was calculated in all patients, according to the formula of APRI = [{current AST level (U/L)/ upper limit of normal AST level (U/L)} X100]/ PLT level (10^9/L). In addition, a Fibroscan was carried out in all patients. The fibrosis score was defined with both APRI score and Fibroscan results which are mentioned below:

HCV-RNA viral loading test, complete blood count (CBC), liver function tests, alpha-fetoprotein (AFP), Fibroscan, and abdominal ultrasound were performed in all patients before starting the DAA treatment. Although, CBC and liver function tests were repeated at 4, 8, and 12th week of the DAA treatment. Final, viral loading tests were completed at 4th week of the treatment and 12 weeks after the treatment.

Sofosbuvir 400 mg/Ledipasvir 90 mg was given to the patients for 8, 12, and 24 weeks with or without ribavirin. To register the side effect of DAA treatment, recording notebooks were given to the patients with instructions to use. The clinical diagnosis was established based on the physician's examination and test results.

Statistical analysis

The ages of the patients in the non-cirrhotic and cirrhotic groups were compared using independent t-tests. Likewise, chi-square tests were used to compare gender for these groups. The mean of AST, ALT, PLT, GGT, and Alb values for each group at each time were checked for outliers and missing data. The main effects of time, diagnostic type and their interaction were determined using a mixed two-way ANOVA with a Greenhouse-Geiser adjustment for lack of sphericity. A critical p-value of < 0.05 was used. The repeated measurements within subjects were then compared to the previous time interval using paired t-tests. The non-cirrhotic and cirrhotic groups' differences at each time interval were tested using the independent t-tests. A Bonferroni-type correction was applied to all t-test results resulting in a significance level set at $p < 0.017$ (= 0.05/3). SPSS version 24 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Ethical statement

The study was approved by the Research Ethics Committee of Mongolian National University of Medical Sciences, with the number of 2018/3-18.

Results

In this study 1,109 DAA treated people aged 18-84 (56.5 ± 6.34) were surveyed, of whom 339 (30.5%) were male. 852 (76.8%) patients with chronic hepatitis C, CTP A 239 (21.5%), CTP B 18 (1.6%) patients with HCV-induced cirrhosis were enrolled in this study. The below table shows the general characteristics of people who received treatment for HCV (Table 1.) The groups were compared by age, gender, BMI, APRI score, and FibroScan result.

In terms of duration of the DAA treatment with or without ribavirin, 26/1109 (2.34%) received 8 weeks, 975/1109 (87.91%) received 12 weeks, and 108/1109 (9.73%) received 24 weeks. Before treatment Fibroscan analysis 835/1109 (75.29%) randomly identified selected classic F0-F1 390/1109 (35.16%), F2 115/1109 (10.36%), F3 111/1109 (10%), F4 219/1109 (19.55%). In terms of duration of treatment with direct-acting agents (DAAs), 26/1109 (2.34%) received 8 weeks, 975/1109 (87.91%) received 12 weeks, and 108/1109 (9.73%) received 24 weeks.

We enrolled 1109 participants who were divided into two groups, non-cirrhotic and cirrhotic. The mean age was 56.5 ± 6.34 (Table 1). We measured AST (U/L), ALT (U/L), T.Bil (μmol/L), GGT (U/L), ALB (g/l) and PLT (10^3/μl) levels at four-time points (before treatment, 4th week, 8th week and 12th week). Table 2 shows AST levels that were significantly different between groups and time points and the same decrease was observed. Table 3 shows ALT levels, the mean level was 65.35 ± 58.46 for the non-cirrhotic group and 126.20 ± 93.5 for the cirrhotic group. Those measurements were statistically significant after treatment. Table 4 indicated that T.Bil level after treatment dropped significantly at 8th week and 12th week in non-cirrhotic, as well as 4th week in cirrhotic group compared to before treatment. Table 5 shows GGT levels. There was a significant difference between 4th week and 12th week in the cirrhotic group.

Table 6 and 7 shows ALB and PLT levels in which ALB levels were significantly decreased during treatment in the 4th and 8th week in the non-cirrhotic group as well as a similar decrease was observed in PLT levels at the 8th week in the non-cirrhotic, and the 12th week compared to before treatment and the 4th

Table 1. General characteristics.

Variables	Non-cirrhosis (n = 852)	Cirrhosis (n = 257)	Total (n = 1109)	p - value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age, years	52.3 ± 13.3	57.5 ± 10.4	56.5 ± 6.34	0.000
BMI	26.9 ± 3.95	27.8 ± 4.05	29.7 ± 0.64	0.001
APRI score	0.66 ± 1.05	2.57 ± 2.51	2.02 ± 0.35	0.000
Fibroscan (kPa)	7.69 ± 4.19	21.50 ± 12.23	11.33 ± 9.54	0.000
	N (%)	N (%)	N (%)	
Gender				
Male	258 (30.3)	81 (31.4)	339 (29.6)	0.801
Female	594 (69.7)	176 (68.6)	770 (69.4)	

Notes: The mean age, APRI score, BMI and Fibroscan result were significantly different between the two groups by t-test. There was no statistically significant difference between the two groups regarding their gender using the Chi-square test.

Table 2. Aspartate Aminotransferase.

Variable	Non-cirrhotic [a, b, c, d] (n = 852)	Cirrhotic [e, f] (n = 257)	Total (n = 1109)	*p - value
AST (U/L)	Mean ± SD	Mean ± SD	Mean ± SD	
Before treatment	51.03 ± 38.51	110.08±68.21	64.75 ± 53.3	0.000
4th week	21.4 ± 8.56	33.01±17.42	24.22 ± 12.3	0.000
8th week	20.73 ± 8.34	32.82±19.74	25.70 ± 16.17	0.001
12th week	20.66 ± 7.63	32.18±19.12	24.25 ± 13.9	0.000

Two-way mixed ANOVA results: Interaction of time and diagnosis F (1.911, 336.37) = 24.194, $p < 0.003$; Main effect of time F (1.912, 327.45) = 334.31, $p < 0.002$; Main effect of diagnosis F(1,186) = 0.561, p = 0.631; *Independent t-test, non-cirrhotic vs. cirrhotic; Paired t-test: [a]before treatment vs. 4th, $p < 0.000$; [b]before treatment vs. 8th, $p < 0.001$; [c]4th vs. 8th, $p < 0.050$; [d]before treatment vs. 12th, $p < 0.000$; [e]before treatment vs. 4th, $p < 0.006$; [f]8th vs. 12th, $p < 0.000$.

Table 3. Alanine aminotransferase.

Variable	Non-cirrhotic [a, b, c] (n = 852)	Cirrhotic [d, e] (n = 257)	Total (n = 1109)	*p - value
ALT (U/L)	Mean ± SD	Mean ± SD	Mean ± SD	
Before treatment	65.35 ± 58.46	126.20 ± 93.5	263.61 ± 5.62	0.000
4th week	22.54 ± 13.09	34.39 ± 26.74	14.29 ± 2.37	0.000
8th week	21.62 ± 13.41	33.88 ± 30.59	26.87 ± 24.52	0.041
12th week	20.91 ± 13.56	34.58 ± 30.4	12.01 ± 3.09	0.000

Two-way mixed ANOVA results: Interaction of time and diagnosis F (1.916, 336.36) = 23.194, $p < 0.001$; Main effect of time F (1.912, 337.45) = 334.31, $p < 0.000$; Main effect of diagnosis F(1,186) = 0.462, p = 0.716; *Independent t-test, non-cirrhotic vs. cirrhotic; Paired t-test: [a]before treatment vs 4th, $p < 0.001$; [b]8th vs. 12th, $p < 0.051$; [c]4th vs. 12th, $p < 0.031$; [d]before treatment vs 8th, $p < 0.002$; [e]before treatment vs 12th, $p < 0.000$.

week vs 12th week in the cirrhotic group. A total of 852 patients with HCV who were diagnosed as non-cirrhosis were surveyed, and the HCV-RNA log10 IU/ml (5.99 ± 0.89) average load was 3,012,366 IU/mL. Table 3 shows test results before treatment, during treatment of the fourth week, treatment of the eighth week, treatment of the twelth week, and after treatment. Test of before treatment and after treatment analyzes were stayistically performed by Steward and one-way ANOVA Greenhouse-Geisser analysis to determine whether there was a statistical time difference and it was decreased (p = 0.002).

Table 4. Total bilirubin.

Variable	Non-cirrhotic [a, b] (n = 852)	Cirrhotic [c, d, e] (n = 257)	Total (n = 1109)	*p - value
T.BILI (μmol/L)	Mean ± SD	Mean ± SD	Mean ± SD	
Before treatment	15.21 ± 7.07	20.76 ± 10.1	18.61 ± 3.25	0.000
4th week	14.03 ± 8.59	22.36 ± 15.04	18.20 ± 11.81	0.007
8th week	15.40 ± 10.58	19.93 ±10.17	16.62 ± 7.37	0.001
12th week	14.74 ± 10.84	17.87 ±9.52	17.07 ± 16.07	0.000

Two-way mixed ANOVA results: Interaction of time and diagnosis F (1.911, 336.37) = 24.194, p < 0.012; Main effect of time F (1.912, 327.45) = 334.31, p < 0.001; Main effect of diagnosis F(1,186) = 0.561, p = 0.631; *Independent t-test, non-cirrhotic vs. cirrhotic; Paired t-test: [a]before treatment vs. 8th, p < 0.000; [b]before treatment vs. 12th, p < 0.000; [c]8th vs. 12th, p < 0.001; [d]before treatment vs. 4th, p < 0.000; [e]before treatment vs. 8th, p < 0.009.

Table 5. Gamma-Glutamyl Transferase.

Variable	Non-cirrhotic [a, b] (n = 852)	Cirrhotic [c, d] (n = 257)	Total (n = 1109)	*p - value
GGT (U/L)	Mean ± SD	Mean ± SD	Mean ± SD	
Before treatment	47.82 ± 40.09	104.63 ± 90.61	71.09 ± 18.12	0.000
4th week	35.46 ± 30.47	58.74 ± 39.02	53.37 ± 4.77	0.000
8th week	28.36 ± 22.48	46.69 ± 38.37	37.52 ± 30.43	0.004
12th week	29.32 ± 23.36	42.98 ± 30.27	30.21 ± 6.89	0.000

Two-way mixed ANOVA results: Interaction of time and diagnosis F (1.961, 336.37) = 24.194, p < 0.072; Main effect of time F (1.911, 327.45) = 334.31, p < 0.009; Main effect of diagnosis F(1,186) = 0.461, p = 0.651; *Independent t-test, non-cirrhotic vs. cirrhotic; Paired t-test: [a]before treatment vs. 4th, p < 0.001; [b]before treatment vs. 12th, p < 0.006; [c]4th vs. 12th, p < 0.000; [d]before treatment vs. 12th, p < 0.056.

Table 6. Albumin.

Variable	Non-cirrhotic [a, b, c] (n = 852)	Cirrhotic [d, e] (n = 257)	Total (n = 1109)	*p - value
ALB (g/l)	Mean ± SD	Mean ± SD	Mean ± SD	
Before treatment	43.06 ± 3.61	40.04 ± 5.04	43.97 ± 1.44	0.000
4th week	42.93 ± 3.07	41.01 ± 4.38	44.52 ± 0.51	0.000
8th week	42.87 ± 3.82	41.30 ± 4.64	42.09 ± 4.23	0.002
12th week	43.13 ± 3.59	41.27 ± 4.35	46.36 ± 2.43	0.000

Two-way mixed ANOVA results: Interaction of time and diagnosis F (1.961, 336.37) = 24.194, p < 0.063; Main effect of time F (1.962, 327.45) = 334.31, p < 0.004; Main effect of diagnosis F(1,196) = 0.561, p = 0.656; *Independent t-test, non-cirrhotic vs. cirrhotic; Paired t-test: [a]before treatment vs. 8th, p < 0.000; [b]before treatment vs. 12th, p < 0.000; [c]8th vs. 12th, p < 0.001; [d]before treatment vs. 4th, p < 0.001; [e]before treatment vs. 8th, p < 0.002.

The table shows the changes in the clinical pharmacological analysis of patients diagnosed with HCV cirrhosis. There were more changes in pre-treatment analysis in patients with cirrhosis than in patients without cirrhosis, and a decrease from the previous level after treatment indicated that the asserted treatment was effective.

We contacted our patients by phone to get information about side effects during treatment. There were 923/1109 (83.2%) who had no drug-related adverse events during the course of the treatment, 154/1109 (13.8%) 1 drug-related adverse events, and 44/1109 (3.9%) 2 and more than 2 drug-related adverse events. If there was no hepatocellular carcinoma before treatment. At the end of the first month of treatment 2/1109 (0.1%) patients with HCC, and after the end of the drug

Table 7. Platelet.

Variable	Non-cirrhotic [a, b] (n = 852)	Cirrhotic [c, d, e] (n = 257)	Total (n = 1109)	*p - value
PLT (10^3/μl)	Mean ± SD	Mean ± SD	Mean ± SD	
Before treatment	219.03 ± 54.46	138.46 ± 56.31	181.96 ± 43.5	0.000
4th week	219.53 ± 54.1	151.49 ± 63.8	232.70 ± 19.44	0.000
8th week	225.37 ± 98.1	153.29 ± 61.7	189.33 ± 79.9	0.004
12th week	221.57 ± 50.08	156.34 ± 64.3	193.72 ± 43.11	0.000

Two-way mixed ANOVA results: Interaction of time and diagnosis F (1.911, 336.37) = 24.194, $p < 0.002$; Main effect of time F (1.962, 327.45) = 334.31, $p < 0.001$; Main effect of diagnosis F(1,186) = 0.461, p = 0.621; *Independent t-test, non-cirrhotic vs. cirrhotic; Paired t-test: [a]before treatment vs. 4th, $p < 0.006$; [b]before treatment vs. 8th, $p < 0.000$; [c]before treatment vs. 4th, $p < 0.011$; [d]before treatment vs. 12th, $p < 0.000$; [e]4th vs. 12th, $p < 0.000$.

treatment 5/1109 (0.4%) patients with HCC were treated. In the fourth week of treatment, two patients with HCC underwent RFA treatment for liver cancer and then continued HCV treatment. In patients treated with Sofosbuvir/Ledipasvir 12 weeks after the end of treatment, the sustained viral load (SVR12) was 97.9% (1086/1109). SVR12 was 99.2% (845/851) in HCV-infected non-cirrhotic patients, SVR12 (241/258) was 93.4% in patients with cirrhosis. SVR12 (19/25) was 76% effective in patients at 12 weeks of treatment with Sofosbuvir 400mg/ Daclatasvir 60 mg. 23/1109 (2.07%) of patients had viral recurrence after treatment.

Using the clinical cohort study model from January 2016 to December 2018, there were 852/1109 (76.8%) with chronic hepatitis C, CTP A 239/1109 (21.5%) with HCV-induced cirrhosis, and CTP B 18/1109 (1.6%) diagnosed included in the study. According to the age group, 38/1109 (3.42%) of the total participants were under 29 years old, 147/1109 (13.25%) were 30-39 years old, 216/1109 (19.4%) were 40-49 years old, 308/1109 (27.7%) were 50-59 years old, and 400/1109 (36.06%) over the age of 60 surveyed. Before treatment, 840/1109 (75.7%) were surveyed in fibroscan analysis.

Discussion

In the past few years, antiviral therapy against HCV infection has evolved significantly. Especially the development of the host targeting agents acting against NS3 protease, NS5A and the NS5B polymerase of the virus has resulted nowadays in more than a 90% cure rate in patients with chronic HCV infection. DAAs are highly effective, interferon-free oral drugs for patients with chronic HCV and cirrhosis patients [12-16]. There are number of DAAs which are approved by the FDA. A liver-targeted nucleotide prodrug of the active triphosphate GS-461203, sofosbuvir inhibits HCV NS5B RNA-dependent RNA polymerase and is used in HCV genotypes 1–4. On the other hand, ledipasvir is an inhibitor of hyperphosphorylation of HCV NS5A, a viral phosphoprotein that plays an important role in viral replication, assembly, and secretion. Therefore, the combination of these DAAs shows additive or synergetic effects against HCV.

Kowdley et al. demonstrated that SVR was 94% after 8 weeks of ledipasvir–sofosbuvir and 95% after a 12-week treatment. While an 8-week treatment of ledipasvir–sofosbuvir plus ribavirin resulted in 1 percentage point lower SVR than the ledipasvir–sofosbuvir only group [17]. The phase 3, randomized, open-label study conducted by Afdhal et al. showed a 94% SVR after 12 weeks of ledipasvir–sofosbuvir treatment group and 96% in the group that received 12 weeks of ledipasvir–sofosbuvir and ribavirin. These rates were increased further to 99% in both 24 weeks of ledipasvir–sofosbuvir and ledipasvir–sofosbuvir and ribavirin groups [11]. An Egyptian study performed on 200 chronic hepatitis C patients revealed a 98% cure rate (negative PCR) in patients who received 12-24 weeks treatment with ledipasvir–sofosbuvir, however, the cure percentage was decreased when ledipasvir–sofosbuvir plus ribavirin was administered in 24 weeks [18]. Furthermore, a prospective observational study in Japanese patients showed a 98.1% SVR of patients in the genotype 1 group treated with ledipasvir/sofosbuvir, and 100% in the genotype 2 group treated with sofosbuvir/ribavirin after a 12-week treatment. Moreover, Mac-2-binding protein glycosylation isomer M2BPGi level significantly decreased at week 48 after treatment initiation [19]. There are several studies conducted on children and

adolescents with chronic HCV. Patients from 6 to 18 years old with genotype 1 and 4 treated with ledipasvir/sofosbuvir had become 100% PCR negative after six weeks of treatment and all patients maintained a sustained virological response at 12 weeks [20].

In our present study, for patients treated with Sofosbuvir/Ledipasvir 12 weeks after the end of treatment, the sustained virological response (SVR12) was 97.7% (1095/1120). These SVR rates are similar to the studies mentioned above. Moreover, SVR12 was 99.2% (846/852) in HCV-infected non-cirrhotic patients, SVR12 (241/258) was 93.4% in patients with cirrhosis, SVR 12 (8/10) was 80% among patients treated for liver cancer.

Moreover, our study showed that the SVR12 was 76% in DAA failure patients retreated with SOF/Dac and the lower SVR12 could be related to HCV genotype because we did not determine the HCV genotype in all of the CHC patients due to the previous evidence [18]. So, additional study is needed to define the HCV genotype in patients with DAA failure in Mongolia. As well, long term follow-up study is demanded to estimate the association between DAA treatment and the recurrence and occurrence of HCC in DAA treated patients with HCC history.

Abdelaty et al. demonstrated that non-cirrhotic naïve patients with chronic HCV genotype 4 infection resulted in a SVR12 of 98% and 96% for sofosbuvir plus ledipasvir and sofosbuvir plus daclatasvir, respectively. The authors concluded that the 12 weeks treatment regimens of sofosbuvir plus daclatasvir and sofosbuvir plus ledipasvir were both efficacious and well-tolerated in patients with HCV genotype 4 infections [21]. On the other hand, another study conducted in naive patients with and without compensated cirrhosis at 15 sites in Canada resulted in a 89% SVR12. Of the 39 patients with cirrhosis, 31 (79%) achieved SVR12, compared with 68 of 72 (94%) patients without cirrhosis [22]. In the meta-analysis including 49 studies from 15 countries for virologic response to direct-acting antiviral therapy in patients with chronic hepatitis C and HCC, the pooled SVR was lower in patients with HCC than in those without HCC (89.6% vs. 93.3%, $p = 0.0012$). SVR was significantly lower in patients with active/residual HCC (73.1%) compared to inactive/ablated HCC (92.6%). As for specific DAA regimens, patients with HCC treated with ledipasvir/sofosbuvir had lower SVR rates than patients without HCC (92.6% vs 97.8%, $p = 0.026$), but heterogeneity was high ($I2 = 84.7\%$, $p < 0.001$) [23]. According to the Hepatitis Prevention, Control and Elimination Program of the Mongolian government from January 2016, there were more than 10,000 patients treated with brand SOF/LDV for genotype 1 HCV between December 2015 and June 2019, and 5,449 patients completed follow-up for 12 weeks after the EOT. After excluding 421 patients, 5,028 patients who met the inclusion criteria were retrospectively analyzed. Between 2015 to 2019, 23 (0.5%) and 5,005 patients (99.5%) with genotype 1a and 1b HCV, respectively, were treated with a fixed-dose tablet containing 90 mg ledipasvir and 400 mg sofosbuvir for 12 weeks, and 81 patients (1.6%) with previous experience of interferon (IFN)-based treatment received additional 1,000 mg ribavirin. HCV RNA was measured at 4, 12, and 24 weeks after the first dose to determine rapid virologic response, end of treatment response (ETR), and sustained virologic response at 12 weeks after end of treatment (SVR12) [24].

A limitattion to this study was that there were several patients excluded from the study by inclusion due to liver cancer diagnosis and treatment. Our numbers were limited by the 1120 patients undergoing treatment at the Liver Center between 2016 and December 2019. Furthermore, studies should be done across various hospitals in different regions. In addition, our study showed that the SVR12 was 76% in DAA failure patients re-treated with SOF/Dac and the lower SVR12 could be related to HCV genotype because we did not determine the HCV genotype in all of CHC patients due to the previous evidence [18]. Thus, additional study is needed to define the HCV genotype in patients with DAA failure in Mongolia. As well, long term follow-up study is required to estimate the association between DAA treatment and the recurrence and occurrence of HCC in DAA treated patients with HCC history.

Conclusions

SVR12 rates in non-cirrhotic and cirrhotic patients were 99.2%, 93.4%, respectively, after DAA treatment. As for patients with viral relapse, 76% of them were successfully retreated with second-line DAA treatment. During the DAA treatment, only 17.6% of all patients had some advanced effects related to DAA treatment, thus, DAA treatment is suitable to Mongolian patients with less advanced effects.

Conflict of Interest

The authors state that there is no conflict of interest.

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