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Research Article

Analysis of Direct Acting Antiviral Agents for Hepatitis C in Macau Government Hospital: The Difficult Enemy, Genotype 3

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Abstract

Background: In 2013, direct antiviral agents were available, we aim to review the efficiency systemically in Macau Government Hospital.

Methods: We retrospectively reviewed the electronic medical records of patients with Hepatitis C treated with direct acting antiviral agents in out-patient clinic from 2016/August to 2019/July.

Results: There were 338 cases included. 174 were women and 164 were men. Genotype 1b, 6 are more common, followed by genotype 1 and 3. Within 8 regimens, 6 got SVR12 over 90%, except daclatasvir + sofosbavir with or without ribavirin (78.6%) and sofosbuvir with ribavirin (0%) group. These 2 groups mostly treated HCV genotype 3. In post treatment analysis, it showed genotype 3 contributed 69% cases of failing to achieve SVR12. Even so, post treatment analysis showed the laboratory of liver enzyme and fibroscan improved. There were no fatal adverse effects noted. Still there were 4 cases of de novo hepatocellular carcinoma, 3 of them occurred within 12 months after treatment.

Conclusions: For the genotype 3, pangenotypic direct acting antiviral agents should be considered. Despite of the viral clearance after treatment, it is still necessary to have long-term follow-up due to risk of advanced liver disease.

Keywords: *Antiviral Agents; Hepatitis C; Genotype 3; Macau; Pangenotypic*

Introduction

Hepatitis C was firstly described as non-A non-B hepatitis. About 70% patients were asymptomatic. However, over 3/4 patients became chronic infection, leading to liver cirrhosis or hepatocellular carcinoma. There are genotypes 1 to 6 and the genotypes prevalence was different between countries [1]. Although no formal systemic review about prevalence of hepatitis C infection in Macau was published, the prevalence in China was about 0.29-0.53% [2,3]. A decade ago, interferon-based therapy was still the mainstream and was not tolerated by some patients. The sustained virological response (SVR) rates of interferon-based therapy were about 40-80%. In recent years, direct antiviral agents (DAAs), targeting three proteins involved HCV lifestyle, were available and the treatment sustained virological response in

over 90% [4]. More and more Hepatitis C patients received DAAs in Macao, echoing the targets for HCV elimination set by WHO [17]. The American Association for the Study of Liver Disease (AASLD 2018) suggests velpatasvir/sofosbuvir (VPV/SOF) or glecaprevir/pibrentasvir (GCV/PBV) to be the first choice for genotype 3 HCV, while the Asian-Pacific Association of the Study of the Liver (APASL) recommends daclatasvir/sofosbavir (SOF/DCV) [5,18]. However, SVR rates are less in HCV genotype 3-infected patients compared to other genotypes. In China, VPV/SOF is the mainstream regimen according to the availability [23]. We aim to review the clinical data and analyses about the HCV treated with DAAs in Macau.

Materials and Methods

First, the study was approved by the ethics committee of Centro Hospitalar Conde de São Januário (CHCSJ). Chronic hepatitis C patients who followed up in infectious specialist out-patient department with DAA prescribed were collected during 2016/August and 2019/July. Total 348 cases found, 10 cases loss follow have complete blood analysis. We included 338 cases.

Prior to DAA therapy, baseline biochemical blood analysis was obtained, together with other co-infection, liver cirrhosis by imaging assessment and HCV RNA viral load and genotype. Blood sampling were arranged at baseline, initial period of treatment, end of treatment and over 12 weeks follow up after the end of treatment. Liver cirrhosis was defined by ultrasound or fibroscan.

The available DAA regimens included ledipasvir/sofosbuvir (LDV/SOF), ombitasvir/ paritaprevir/ritonavir/dasabuvir (PrOD), velpatasvir/sofosbuvir (VPV/SOF), glecaprevir/pibrentasvir (GCV/PBV), daclatasvir+sofosbavir (DCV+SOF), daclatasvir/asunaprevir (DCV/ASV), sofosbavir(SOF), and elbasvir/grazoprevir (EBR/GZR). All the regimens may be or may not be with ribavirin. The number of patients received each regimen are listed in table 1.

	LDV/SOF±RBV	PrOD±RBV	VPV/SOF±RBV	GCV/PBV	DCV+SOF	DCV/ASV	SOF+RBV	EBR/GZR
Patient, Number (%)	232 (68.8)	38(11.3)	23(6.8)	11(3.3)	28(8.3)	1(0.3)	3(0.9)	2(0.6)
DAA, direct-acting antiviral agent; LDV/SOF, ledipasvir/sofosbuvir; PrOD, ombitasvir/paritaprevir/ritonavir/ dasabuvir; VPV/SOF, velpatasvir/sofosbuvir; GCV/PBV, glecaprevir/pibrentasvir; DCV+SOF, daclatasvir +sofosbavir; DCV/ASV, daclatasvir/asunaprevir; RBV, ribavirin. EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; RBV, ribavirin.								

Table 1: *The number of patient in each DAA group.*

Other population data including route of transmission, co-infection situation, and liver cirrhosis status were obtained from the CHCSJ medical systems. The statistical analysis relied on student's t test and the chi-square test to compare the two groups. P values smaller than 0.05 were considered significant.

Results

The demographic data were shown here in different regimens groups in table 2. Altogether 338 cases were analyzed, including 174 women and 164 men, and 5 cases belonged to second DAA treatment. For the ledipasvir/ sofosbuvir with or without ribavirin regimens, the average age was 62.0 (± 11.1) years. 44% of them are male. Nearly half of them got transfusion history. 47.9% of this group had previous treatment and 51.7% were treatment naïve. Baseline log10 viral load was 6.1 (± 0.9) IU/ml.

	LDV/ SOF±RBV	PrOD±RBV	VPV/ SOF±RBV	GCV/PBV	DCV+SOF±RBV	DCV/ASV	SOF+RBV	EBR/GZR
Age, mean (SD)	62.0(11.1)	62.5(12.7)	57.8(11.9)	54.6(12.1)	54.0(10.0)	58.0(17.0)	54.0(7.5)	74.5(4.9)
Sex, N (%)								
Male	102(44.0)	16(42.1)	17(73.9)	8(72.7)	19(67.9)	0	1(33.3)	1(50.0)
Female	130(56.0)	22(57.9)	6(26.1)	3(27.3)	9(32.1)	1(100)	2(66.7)	1(50.0)
Risk factors, N (%)								
Transfusion	116(49.6)	13(33.3)	6(22.2)	3(27.3)	2(6.9)	1(100)	1(33.3)	1(50.0)
IVDU	42(17.9)	6(15.4)	12(44.4)	7(63.6)	17(58.6)	0	1(33.3)	1(50.0)
Sexual transmitted	5(2.1)	1(2.5)	2(7.4)	0(0.0)	1(3.4)	0(0)	0(0)	0(0)
Unknown	72(30.8)	19(48.7)	7(25.9)	1(9.1)	9(31.0)	0(0)	1(33.3)	0(0)
Previous AVT, N (%)								
Relapse	51(22.0)	6(15.8)	3(13)	1(8.3)	6(21.4)	0	1(33.3)	0(0)
Incomplete	61(26.3)	13(34.2)	2(9.0)	1(8.3)	8(28.6)	0(0)	1(33.3)	0(0)
Treatment naïve	120(51.7)	19(50.0)	18(78.3)	10(83.3)	14(50.0)	1(100)	1(33.3)	2(100)
Baseline Log $_{10}$ HCV viral load IU/ml, mean (SD)	6.1(0.9)	6.1(1.0)	6.1(1.0)	6.0(1.1)	6.3(0.6)	6.8(0)	6.1(0.3)	6.4(1.2)
Liver cirrhosis, N (%)	67(28.6)	10(26.3)	7(25.9)	8(66.7)	14(50.0)	1(100)	2(66.7)	0(0)
Pre-DAA AST (U/L), mean (SD)	66.8(46.8)	53.3(28.2)	56.3(36.3)	89.3(69.5)	88.3(49.9)	63(0)	80.3 (38.5)	23.5(4.9)
Pre-DAA ALT (U/L), mean (SD)	78.8(62.2)	62.4(40.1)	60.9(45.9)	88.5(75.6)	102.6(81.5)	100(0)	64.0 (42.5)	19.5 (10.6)
Pre-DAA Tbil (umol/l), mean (SD)	15.5(17.2)	11.7(5.2)	15.8(10.8)	12(6.4)	13.5(6.4)	12(0))	14.0(2.0)	11(0)
HCC, N	13	1	1	0	1	0	0	0
With HBV, N	15	4	5	1	6	0	0	0
With HIV, N	7	0	1	0	2	0	0	0

Table 2: *Demographic data of different groups.*

DAA, direct-acting antiviral agent; LDV/SOF, ledipasvir/sofosbuvir; PrOD, ombitasvir/paritaprevir/ritonavir/ dasabuvir; VPV/SOF, Velpatasvir/Sofosbuvir; GCV/PBV, glecaprevir/pibrentasvir; DCV+SOF, daclatasvir +sofosbavir; DCV/ASV, daclatasvir/asunaprevir; RBV, ribavirin. EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; RBV, ribavirin. N, number; SD, standard deviation; Tbil, total bilirubin; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

For the PrOD group with or without ribavirin regimens, the average age was 62.5 (± 12.7) years. 42% of them are male. One third of them got transfusion history. For the VPV/SOF, GCV/PBV and DCV+SOF group, the average age was below 60 years, > 60% was male and

almost half of them got intravenous drug abuse history. The GCV/PBV and DCV+SOF group even got at least 50% the patients with cirrhosis. There are less than 5 patients within our study treated with DCV/ASV or plus EBR/GZR.

As for the genotype distribution in this study, as shown in figure 1, genotype 1b and 6 occupied 37.2% and 31.9% respectively, followed by genotype 1 (12.1%) and genotype 3(11.8%). There are 3 cases experienced genotype changing. One case shifted from genotype 2 to 1, one from 1a to 6, and one from 6 to 1b. 2 (66.7%) of them had exposure of IV drug use. There is one case with genotype 1a and 1b at the same time.

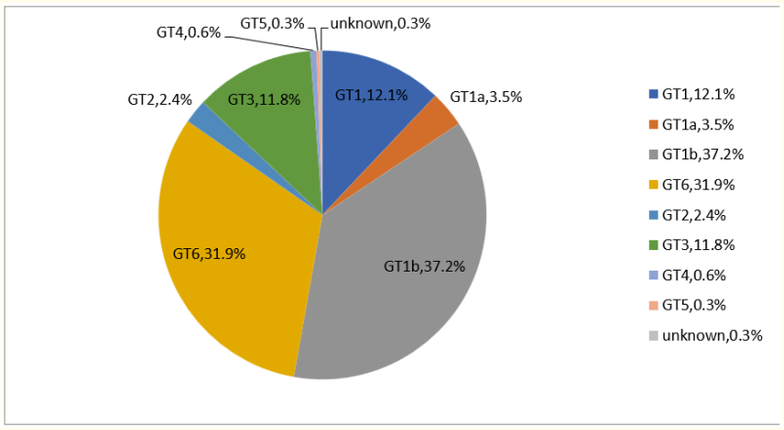

Figure 1: *The number of patient in each DAA group.*

Post treatment analysis

The sustained virological response at 12 weeks after treatment finished (SVR 12) rates were grafted as figure 2. The SVR 12 rate of LDV/SOF with or without ribavirin was 99.1%, PrOD with or without ribavirin was 97.4%, VPV/SOF with or without ribavirin was 91.3%, GCV/PBV was 90.9%; DCV+SOF with or without ribavirin was 78.6%; sofosbuvir with ribavirin was 0%, DCV/ASV was 100%, and EBR/GZR was 100%. Although a majority achieve SVR over 90%, there are cases fail to obtain SVR 12, as shown in figure 2. For the regimens with low SVR 12, DCV+SOF with or without ribavirin and sofosbuvir with ribavirin group included 78% and 100% genotype 3 HCV patients, respectively. Overall, the genotype distribution of failure SVR 12 was grafted as figure 3, which showed occupied 69%.

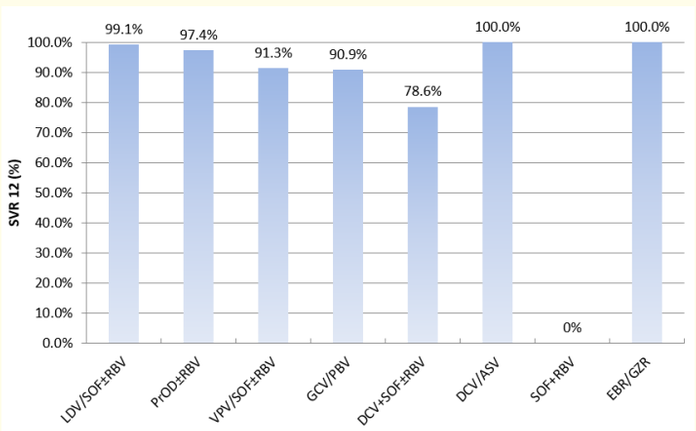

Figure 2: The SVR12 rates of each group.

LDV/SOF, ledipasvir/sofosbuvir; PrOD, ombitasvir/paritaprevir/ ritonavir/ dasabuvir; VPV/SOF, velpatasvir/sofosbuvir; GCV/PBV, glecaprevir/pibrentasvir; DCV+SOF, daclatasvir +sofosbavir; DCV/ASV, daclatasvir/asunaprevir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; RBV, ribavirin. SVR, sustained virological response.

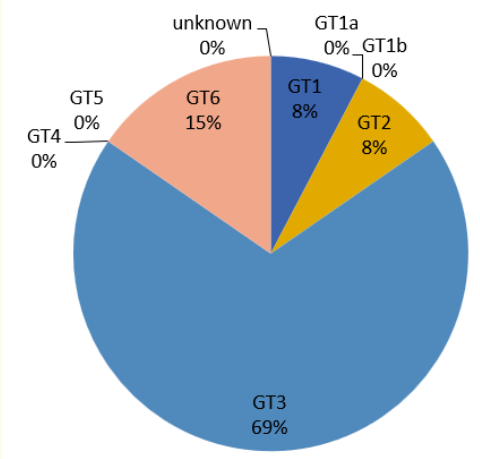

Figure 3: *Genotype (GT) distribution of failure to achieve SVR 12. Genotype 3 accounts for 69% of all failure cases.*

After treatment, the laboratory changes are listed in table 3 to compare the pre and post DAA treatment situation. AST decreased from 66.6 ± 45.9 to 29.0 ± 27.8 U/l. ALT decreased from 77.5 ± 61.6 to 24.9 ± 28.0 U/l. Total bilirubin dropped from 14.7 ± 14.8 to 12.7 ± 7.1. For those with follow up fibroscan, the level dropped from 12.1 ± 9.1 to 8.4 ± 5.5 KPa. The laboratory finding showed significant improvement about liver enzyme and liver fibrosis, but the AFP level was not significantly improved compared to pre-DAA group. Averagely, the duration for liver enzyme normalization was 8.3 weeks after treatment started, and 6.3 weeks for HCV RNA clearance.

Mean (S.D)	Pre-DAA	Post-DAA	*P* value
AST(U/L)	66.6 (45.9)	29.0 (27.8)	< .001
ALT(U/L)	77.5 (61.5)	24.9 (28.0)	< .001
Tbil (umol/l)	14.7 (14.8)	12.7 (7.1)	0.01
Dbil (umol/l)	10.4 (4.4)	9.4 (6.0)	0.18
Fibroscan (KPa)	12.1 (9.1)	8.4 (5.5)	< .001
AFP (ng/ml)	21.1(189.3)	11.9(91.7)	0.21

Table 3: *Comparison of laboratory data between pre and post DAA treatment.*

Tbil, total bilirubin; Dbil, direct bilirubin; DAA, direct active antiviral agents; AFP, alpha-fetal protein.

We further compared the HCV genotype 3 with other genotypes, as shown in table 4. The patient was significantly younger (53.3 vs 61.1 years old), and male predominant, and more HBV coinfection (80.5% vs 56.1%). As for the exposure history, there were less transfusion history and more intravenous drug use history in genotype 3 group. No matter which genotype, there was no significant difference about pre-treatment baseline viral load. However, the baseline fibroscan showed higher liver pressure in genotype 3 group (17.0 vs12.0 KPa), also the rate of liver cirrhosis was higher in genotype 3 group. After DAA treatment, genotype 3 group got lower SVR 12 compared to other HCV genotypes.

	Genotype 3	non-genotype 3	*P* value
Age, mean (S.D)	53.3(9.9)	61.1(11.6)	<.001
Male	80.5%	56.1%	0.002
With HBV	22.2%	9.6%	0.02
With HIV	8.3%	3.3%	0.14
Risk factors			
Transfusion	8.3%	43.6%	<.001
Sexual transmitted disease	2.7%	3%	0.94
Intravenous drug use	72.2%	27.7%	<.001
Liver cirrhosis	52.8%	32.3%	0.02
Pre-DAA HCC	5.5%	5%	0.88
Pre-DAA fibroscan (KPa)	17.0(12.4)	12.0(8.7)	0.043
post-DAA fibroscan (KPa)	12.6(8.51)	7.86(5.7)	0.09
Baseline Log 10 HCV viral load IU/ml,mean (SD)	6.0(0.8)	6.1(0.9)	0.69
Failed SVR 12	22.2%	4.3%	<.001

Table 4: *Comparison of demographic data of genotype (GT) 3 and other genotypes.*

DAA, direct-acting antiviral agent; N, number; SD, standard deviation; T-bil, total-bilirubin; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response.

There were 4 patients who developed de novo hepatocellular carcinoma. The basic data were listed in table 5. In de novo hepatocellular carcinoma, 50% were male, averagely 67.3 years old. 75% of them had cirrhosis at pre-treatment status. Genotype 1b occupied 3 cases. Except the case with genotype 3, other case with de novo hepatocellular carcinoma got SVR 12. The duration after treatment finished was 13.8 months on average. Three of them developed de novo hepatocellular carcinoma within 12 months.

	De novo (N = 4)	Recurrence (N = 3)
Male, N (%)	2(50.0%)	1(33.3%)
Age, mean (S.D)	67.3(13.9)	70.3(3.2)
Liver cirrhosis, N (%)	3(75)	2(66.7)
Genotype, N		
1	0	1
1a	0	0
1b	3	1
2	0	0
3	1	0
4	0	0
5	0	0
6	0	1
SVR12, N (%)	3(75)	3(100)
Months to DAA therapy, mean	13.8(11.8)	

Table 5*: The basic data of the de novo and recurrence hepatocellular carcinoma.*

DAA, direct-acting antiviral agent; N, number; SD, standard deviation; T-bil, total-bilirubin; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response.

Drug adverse effects

There were some non-fatal adverse effects recorded in table 6, including skin rashes, dizziness, headache, and GI symptoms. All of them resolved spontaneously. One patient needed to stop medication (PrOD) before finishing due to fever and one needed to stop LDV/SOF due to edema at 9 weeks of treatment. For laboratory abnormalities, 2 presented with elevated liver enzyme and creatinine elevation. Both of them resolved spontaneously. There are 11 patients with metabolic problem of lipid or uric acid disorder. All of them are transient and without symptoms. 2 patients died of lung cancer and laryngeal cancer after treatment finished.

	LDV/SOF±RBV	PrOD±RBV	VPV/ SOF±RBV	GCV/ PBV	DCV+SOF±RBV	DCV/ASV	SOF+RBV	EBR/GZR
Patient, n	232	38	23	11	28	1	3	1
Total adverse effects, n	28	2	5	2	2	0	0	0
Rash	2	0	0	1	1	0	0	0
GI symptoms	3	0	0	0	0	0	0	0
CNS symptoms (headache, dizziness, blur vision)	3	1	0	0	0	0	0	0
Insomnia	3	0	0	0	0	0	0	0
Myalgia/fatigue	4	0	0	0	0	0	0	0
Edema	1	0	0	0	0	0	0	0
Fever	0	1	0	0	0	0	0	0
Anemia	0	0	0	0	1	0	0	0
Dyslipidemia	4	0	1	0	0	0	0	0
Hyperuricemia	4	0	2	0	0	0	0	0
Elevated creatine kinase (CK)	2	0	2	0	0	0	0	0
Elevated liver enzyme	1	0	0	0	0	0	0	0
Elevated creatinine	0	0	0	1	0	0	0	0
Fatal adverse effects	0	0	0	0	0	0	0	0

Table 6: *Treatment safety data.*

DAA, direct-acting antiviral agent; LDV/SOF, ledipasvir/sofosbuvir; PrOD, ombitasvir/paritaprevir/ritonavir/ dasabuvir; VPV/SOF, Velpatasvir/Sofosbuvir; GCV/PBV, glecaprevir/pibrentasvir; DCV+SOF, daclatasvir +sofosbavir; DCV/ASV, daclatasvir/asunaprevir; RBV, ribavirin. EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; RBV, ribavirin.

Discussions

The DAAs are highly effective and is used more widely in recent years. It is tolerated by most of the patients and the response is satisfactory. The price is one of the main concerns and we need to evaluate the cost-effectiveness of the treatment [5]. The prevalence of different genotype of hepatitis C in Macau is different from mainland China, Korea, and Japan [6]. While there are more and more literatures about hepatitis C in Asian countries, we still need local data to local situation about treating hepatitis C.

Our study showed the regimen for HCV achieved SVR 12 at over 90% of the patients, which is comparable to results in other DAAs real-world data [5-7]. There are also biochemistry responses and histology responses in view of the post treatment improvement shown in the fibroscan data. However, in group that treated with DCV/SOF with or without ribavirin and sofosbuvir with or without ribavirin, the SVR

12 rate was only 78% or even 0%, within the latter all of them treated for genotype 3 HCV. Previous literature has shown sofosbuvir-based DAA regimens cannot provide cost-effective treatment compared to traditional interferon plus ribavirin [5,8]. Whether the pangenotypic DAAs can overcome this problem, we still need more clinical trial and study, especially for those relapses after treatment and with cirrhosis [9].

Our study showed genotype 3 HCV infections are related to younger age, male, and IV drug user. Meanwhile, prevalence of HCV in IV drug user may be more than 50% [10]. In Hong Kong, more male IV drug users get HCV [11]. Although Tao YC., *et al.* showed all sofosbuvir is highly effective in treating genotype 3 HCV in Chinese population, VPV/SOF was the first choice [19]. However, our study also showed genotype 3 with higher rate of cirrhosis, although not significant (P = 0.06). One hypothesis is that hepatic steatosis leads to negative impact of this type, but patients in genotype 3 group usually with less metabolic disease such as diabetes or obese. It is possible that host genetic factor, IL28B CC genotype can explain the relationship between genotype 3 and cirrhosis [20]. Genotype 3 HCV was called "difficult-to-treat" type, with a faster fibrotic liver change and potentially greater risk of hepatocellular carcinoma development [12,14]. GCV/PBV with prolonged treatment was suggested to cirrhotic ones in genotype 3 HCV group [9].

Within 8 relapsed patients (4 in DCV+SOF,1 in SOF+ribavirin, 1 in DCV+SOF +ribavirin, 1 in GCV/PBV, 1 in VPV/SOF), it is still difficult to explain the reasons. Previously it was suggested that genotype 3 cases can be treated with extension of therapy or the addition of ribavirin [16]. However, ASTRAL-3 trial showed 12 weeks VPV/SOF treatment was better than 24 weeks treatment with SOF plus ribavirin. So, there is no definite benefit by adding ribavirin being a strategy for genotype 3 HCV treatments [21]. On the other hand, genotype 3 HCV has high frequencies of the nonstructural protein 5A A30K and Y93H substitutions and the mutations showed as high as 10-fold increase in 50% effect concentration for daclatasvir compared to wild type. It explains the treatment failure and further supports the use of NS3 inhibitors, such as glecaprevir regimen, in combination [22,23].

Although no serious adverse effects were recorded, some literatures raised the problem that DAAs treatment, even with SVR 12, may lead to higher rate of de novo HCC development, compared to traditional interferon-based regimes. However, with DAAs treatment, more cirrhotic patient, especially the decompensated ones who cannot receive interferon-based treatment in the past, got treated. For this bias, the rates of developing hepatocellular carcinoma could be higher in DAA-treated group [13]. As a result, even with SVR 12 achieved, the surveillance is still needed due to report of de novo hepatocellular carcinoma.

This study has several limitations. First, it is a retrospective design, so patients who had poor responses to treatment easily loss follow-up, and this would bias the results of virological and biochemical responses. Second, the diagnosis of cirrhosis was based on imaging or fibroscan criteria, rather than that of histology. Third, there is still no consensus of Ribavirin usage, so its combination was driven by physician's decision. Moreover, the rates of treated by LDV/SOF was higher than other group, the efficacy of different treatment groups may not be compared, especially in different genotypes. Finally, we still need further follow-up to survey about the late onset HCC development or recurrence.

Summary

The SVR12 rates and overall responses in treating Chronic hepatitis C with DAAs in Macau were comparable with other literature in many other countries. For the genotype 3 with character of treatment difficulty, pangenotypic DAAs such as VPV/SOF or GCV/PBV are considered. Although virology and liver enzyme improve in post treatment status, it is still necessary to have long-term follow-up due to risk of advanced liver disease, despite viral clearance.

Disclosure of Interest

The authors do not have any financial relationship which might be viewed as a potential conflict of interest.

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