Clinical outcomes of patients with chronic hepatitis C after generic direct−acting antiviral treatments in Vietnam: A retrospective analysis

Huong TT Vu[1], Azumi Ishizaki[2✉], Quynh T Nguyen[1,2], Huyen N Nguyen[1], Hoi T Le[1], Kinh V Nguyen[1], Hiroshi Ichimura[2]

[1]National Hospital for Tropical Disease, Hanoi, Vietnam

[2]Department of Viral Infection and International Health, Graduate School of Medical Sciences, Kanazawa University, Japan

ABSTRACT

Objective: To evaluate the outcomes of generic direct-acting antiviral treatments for chronic hepatitis C in Vietnam.

Methods: The medical records of 522 patients (median 45 years; Female, 25.3%) with chronic hepatitis C treated at a tertiary hospital in northern Vietnam in 2016 were retrospectively reviewed.

Results: Female patients were significantly older than male patients (median 52, IQR 41-59 *vs*. 43 years, IQR: 39-55; *P*<0.001). Among 522 patients, 49.4% were infected with hepatitis C virus (HCV) genotype 6, followed by 1a (19.0%), 1b (13.0%), and 3 (5.9%). Co-infection with hepatitis B virus or human immunodeficiency virus was noted in 5.8% and 3.1% of patients, respectively. Patients were treated with ledipasvir/sofosbuvir with or without ribavirin (70.9%), sofosbuvir/pegylated-interferon + ribavirin (13.2%), daclatasvir/ sofosbuvir with or without ribavirin (12.5%), or sofosbuvir/ribavirin (3.4%), and 96.4% (*n*=503) completed the direct-acting antiviral treatment. No patient discontinued treatment due to adverse event(s). A sustained virologic response 12 weeks after the end of the treatment (SVR12) was evaluated in 62.6% of patients. Overall sustained virologic response 12 weeks after the end of the treatment was 98.7% regardless of HCV genotypes or direct-acting antiviral regimens. The severity of liver stiffness was significantly decreased from 10.2 to 6.3 kilopascals measured by transient elastography by the treatment (*P*<0.001). Among patients who completed the direct-acting antiviral treatment, 17.7% returned for further follow-ups after SVR12.

Conclusions: In Vietnam, the current generic direct-acting antiviral treatment for chronic hepatitis C was effective regardless of HCV genotypes and direct-acting antiviral regimens with the attenuation of liver stiffness. It is feasible to implement direct-acting antiviral treatment to cure chronic hepatitis C patients at any liver fibrosis stages in Vietnam.

KEYWORDS: Vietnam; Chronic hepatitis C; Generic direct-acting antiviral; Improvement of liver stiffness

1. Introduction

Chronic hepatitis C (CHC) is a huge global public health issue. Approximately 71 million individuals worldwide have CHC, with 399 000 related deaths being reported in 2015[1]. The elimination of viral hepatitis as a public health threat by 2030: reductions in new infections by 90% and mortality by 65% from 2015 to 2030, is a global target that was endorsed by the World Health Assembly in 2016[2]. One of the key interventions to achieve this goal is to increase the number of individuals who are treated for CHC. New oral direct-acting antivirals (DAA) for hepatitis C virus (HCV) are able to cure more than 90% of patients with CHC. The World Health Organization currently recommends treating all patients with CHC who are 12 years or older irrespective of the disease stage with pan-genotypic DAA[3].

In Vietnam, the number of patients with CHC is estimated to be approximately 1 million, which is 1.1% of the general population[4–7], with 5 300 estimated annual deaths due to the sequela of CHC being reported in 2016[8]. The Ministry of Health Vietnam issued a National Action Plan for viral hepatitis prevention and control between 2015 and 2019 and treatment guidelines for CHC in 2016 to expand access to HCV care and treatment in Vietnam[5]. By 2016, approximately 4 500 individuals, accounting for only 0.45% of patients with CHC, had been treated with DAA[9]. The Ministry of Health Vietnam launched a new policy to reimburse 50% of DAA through health insurance from January 2019 in an

attempt to expand the DAA treatment. Vietnam is a country in which mixed HCV genotypes (such as genotypes 1a, 1b, 3, and 6) are circulating[10]. It is important to understand current treatment outcomes in order to build a more effective strategic plan to control CHC in Vietnam; however, limited information is currently available on the outcomes of DAA treatment for Vietnamese CHC in the real-world[11]. Therefore, the aim of the present study was to clarify the current treatment outcomes of CHC with generic DAAs at a tertiary hospital in Hanoi, Vietnam.

2. Materials and methods

2.1. Subjects and methods

The medical records of patients who were treated for CHC at a tertiary hospital in Hanoi, Vietnam, between January 2016 and December 2016 were retrospectively reviewed. The demographic factors of patients, comorbidities, the co-infection status with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV), risk factors related to HCV acquisition, prior HCV treatment history, HCV genotypes at baseline, DAA regimens and treatment durations, laboratory data, the level of liver stiffness assessed by a transient elastography (TE, FibroScan®, Echosens, Paris, France), and HCV viral loads before and 12 weeks after the end of the treatment were extracted from medical records.

The primary endpoint was a sustained virologic response (SVR) 12 weeks after complete treatment (SVR12) with undetectable HCV RNA <15 IU/mL (Cobas® AmpliPrep/COBAS® TaqMan® HCV Qualitative Test, v2.0, Roche, USA). The secondary outcome was a change of the patients' liver stiffness level that was measured using TE, a noninvasive method. Based on the TE score, the liver stiffness level was classified into five stages: F0: TE score <5 kilopascals (kPa); F1: $5 \leqslant$TE score <7.1 kPa; F2: 7.1 $\leqslant$TE score <8.7 kPa; F3: 8.7 $\leqslant$TE score <14.5 kPa; and F4: TE score $\geqslant$14.5 kPa. F4 was defined as "cirrhosis" and F0-F3 as "non-

cirrhosis". Laboratory data at the baseline and during the treatment period and the magnitudes of changes in laboratory values were calculated and graded from grades 1 to 4 according to the Common Terminology Criteria for Adverse Events version 4.03 by the National Cancer Institute in the United States of America (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Grades 3 and 4 were considered to be serious adverse events. Since patient interviews and examinations were not standardized at the time of consultations, the subjective symptoms of patients documented in medical records were not applied to the assessment of serious adverse events in the present study.

2.2. Statistical analysis

Statistical analyses were performed with SPSS version 25. Pearson's *chi*-square test and Fischer's exact test were performed to assess differences in proportions. Mann-Whitney *U* test was used to compare data among the groups. The Friedman test with Bonferroni correction was conducted to compare paired data from baseline. Pearson's product-moment correlation coefficient was used to assess relationships. A *P*-value of less than 0.05 was considered to be significant.

2.3. Ethical consideration

This study protocol was approved by the Ethics Committee of Kanazawa University, Japan (No. 2383-1) and the Ethics Committee of the tertiary hospital in Hanoi, Vietnam (No. 241/NDTW-TCCB).

3. Results

3.1. Demographic and clinical characteristics at baseline

The study flowchart is shown in Figure 1. We recruited all patients (544 patients) who were evaluated the eligibility to treat with
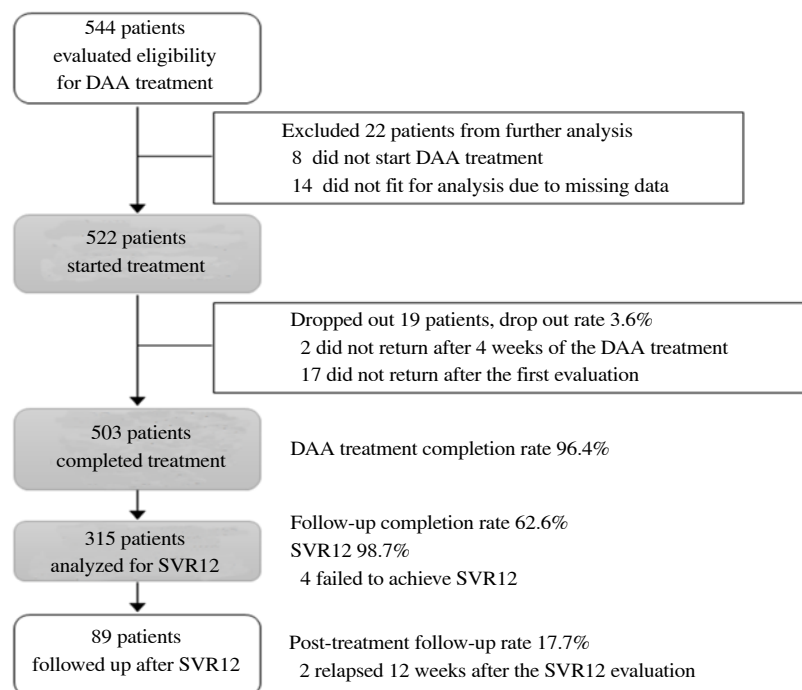

Figure 1. The study flowchart. DAA: direct-acting antivirals; SVR12: sustained virologic response 12 weeks after the end of the treatment.

generic DAAs at the site between January 2016 and December 2016 then excluded 8 patients who did not start DAA treatment and 14 patients whose medical records had missing data and not able to analyze further. Finally, the medical records of 522 patients who were treated with generic DAAs at a tertiary hospital in Hanoi, Vietnam were reviewed (Table 1). There were 132 (25.3%) females and 390 (74.7%) males with a median age of 45 years (interquartile range, IQR: 39-55). Female patients with a median age of 52 years (IQR 41-59) were significantly older than male patients with a median age of 43 years (IQR 38-53) ($P<0.001$).

The median TE score of the patients ($n=476$) whose TE data were available was 8.2 kPa (IQR 6.1-14.8), and 123 (25.8%) had cirrhosis (F4: TE score $\geqslant$14.5 kPa). The TE score correlated with age ($r=0.31$, $P<0.001$), but the TE score did not differ between female and male (Female: median 8.0 kPa, IQR 5.7-15.1; Male: 8.3 kPa, IQR 6.2-14.8, $P=0.38$, Table 1).

Table 1. Demographic and clinical characteristics of 522 patients who started DAA.

Items	n	Total n=522	n	Female (F) n=132	n	Male (M) n=390	U values or χ^2 values F vs. M	P value F vs. M
Age (years), median (IQR)	520	45 (39-55)	132	52 (41-59)	388	43 (38-53)	18 827[a]	<0.001
Residence area (near Hanoi)	522	166 (31.8%)	132	42 (31.8%)	390	124 (31.8%)	<0.001	1.00
Fibrosis stages	476		114		362			
F0		55 (11.6%)		15 (13.2%)		40 (11.0%)	2.25	0.69
F1		130 (27.3%)		35 (30.7%)		95 (26.2%)		
F2		65 (13.7%)		13 (11.4%)		52 (14.4%)		
F3		103 (21.6%)		21 (18.4%)		82 (22.7%)		
F4 (Cirrhosis)		123 (25.8%)		30 (26.3%)		93 (25.7%)		
TE score (kPa), median (IQR)	476	8.2 (6.1-14.8)	114	8.0 (5.7-15.1)	362	8.3 (6.2-14.8)	19 520[a]	0.38
HCV genotypes	522		132		390			
1a		99 (19.0%)		18 (13.6%)		81 (20.8%)	13.366	0.06
1b		68 (13.0%)		17 (12.9%)		51 (13.1%)		
1		12 (2.3%)		3 (2.3%)		9 (2.3%)		
2		16 (3.1%)		6 (4.5%)		10 (2.6%)		
3		31 (5.9%)		4 (3.0%)		27 (6.9%)		
6		258 (49.4%)		79 (59.8%)		179 (45.9%)		
1 and 3		1 (0.2%)		0 (0.0%)		1 (0.3%)		
Unknown		37 (7.1%)		5 (3.8%)		32 (8.2%)		
HCV viral load, IU/mL, median (IQR)	499	1.62×10^6 (3.10×10^5-4.48×10^6)	123	1.97×10^6 (3.01×10^5-4.51×10^6)	376	1.53×10^6 (3.10×10^5-4.41×10^6)	22 966	0.91
Prior HCV treatment with IFN	503	30 (6.0%)	124	10 (8.1%)	379	20 (5.3%)	1.29	0.28
Comorbidity	519	103 (19.8%)*	131	31 (23.7%)	388	72 (18.6%)	1.61	0.21
HBV co-infection	519	30 (5.8%)	131	7 (5.3%)	388	23 (5.9%)	0.06	1.00
HIV co-infection	519	16 (3.1%)	131	3 (2.3%)	388	13 (3.4%)	0.37	0.59

F: female: M: male; IQR: interquartile range; TE: transient elastography measured by Fibroscan®; F0: TE score <5 kPa; F1: 5 $\leqslant$TE score <7.1 kPa; F2: 7.1 $\leqslant$TE score <8.7 kPa; F3: 8.7 $\leqslant$TE score <14.5 kPa; F4: TE score $\geqslant$14.5 kPa; HCV: hepatitis C virus; IFN: interferon; HBV: hepatitis B virus; HIV: human immunodeficiency virus; *: details of the comorbidities of 103 patients: diabetes mellitus, 36/519 (6.9%); cardiovascular disease 26 (5.0%); malignancy 18 (3.5%); thyroid disease 12 (2.3%); renal disease 8 (1.5%); tuberculosis 3 (0.6%); mental disease 2 (0.4%); and others 11 (2.1%). Mann-Whitney U test was applied for age and TE scores ([a]U values); Fishers' exact test was applied for comparisons of other values.

Table 2. Laboratory data of participants at baseline.

Indicators	n	Total	n	Female (F)	n	Male (M)	U value F vs. M	P value F vs. M
Hemoglobin, g/L	498	148 (138-158)	124	136 (126-143)	374	152 (143-161)	8 317	<0.001
Platelet count, $\times10^9$/L	497	191 (146-237)	124	207 (145-245)	373	186 (147-233)	20 899	0.11
INR	452	1.03 (0.98-1.08)	113	1.02 (0.97-1.07)	339	1.03 (0.98-1.09)	17 464	0.16
Glucose, μmol/L	484	5.1 (4.6-5.7)	123	5.1 (4.6-5.6)	361	5.1 (4.6-5.8)	21 084	0.40
Creatinine, μmol/L	489	89 (78-98)	124	76.5 (68-84)	365	92 (83-101)	8 576	<0.001
Total bilirubin, μmol/L	473	12.8 (9.9-16.6)	119	12.6 (9.8-16)	354	12.9 (9.9-16.8)	19 871	0.36
Direct bilirubin, μmol/L	393	4.7 (3.1-6.8)	99	5.0 (3.3-6.8)	294	4.5 (3.1-6.8)	14 322	0.81
Albumin, g/L	261	46 (43-49)	68	46 (42-48)	193	46 (43-49)	6 063	0.35
AST, U/L	494	62 (38-101)	125	57 (34-101)	369	64 (40-101)	20 734	0.09
ALT, U/L	495	87 (48-153)	125	70 (38-133)	370	94 (54-157)	18 309	<0.001
GGT, U/L	483	86 (46-174)	124	49 (19-94)	359	105 (58-207)	11 774	<0.001
AFP, ng/mL	430	5.0 (2.9-11.7)	106	4.1 (2.6-9.6)	324	5.4 (3.0-12.0)	15 100	0.06
TSH, μU/mL	338	1.6 (1.2-2.4)	81	1.6 (1.1-2.5)	257	1.7 (1.2-2.4)	9 883	0.49
FT4, ꝺmol/L	338	15.9 (14.4-17.7)	82	16.1 (14.6 -17.2)	256	15.8 (14.2 -17.8)	10 089	0.60
TE score, kPa	476	8.2 (6.1-14.8)	114	8.0 (5.7-15.3)	362	8.3 (6.2-14.8)	19 520	0.38

Data were expressed as median (IQR). F: female: M: male; IQR: interquartile range; INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; AFP: alpha-fetoprotein; TSH: thyroid-stimulating hormone; FT4: free thyroxine; TE: transient elastography. Mann-Whitney U test was applied to compare values between groups.

Among the 522 patients with CHC, HCV genotype 6 was most commonly detected (49.4%), followed by genotypes 1a (19.0%), 1b (13.0%), and 3 (5.9%). Of the 519 patients whose data of co-infections were available, 30 (5.8%) were co-infected with HBV and 16 (3.1%) with HIV (Table 1). Thirty patients had a history of interferon treatment.

Laboratory data at baseline (before the treatment) showed mild liver injury (Table 2). Hemoglobin, creatinine, alanine aminotransferase, and gamma-glutamyl transferase levels were significantly lower in females than in males and other laboratory data showed no significant difference between females and males.

3.2. DAA treatments and safety

Among the 522 patients with CHC, 370 (70.9%) started treatment with ledipasvir/sofosbuvir with or without ribavirin, 69 (13.2%) with sofosbuvir/pegylated-interferon + ribavirin, 65 (12.5%) with daclatasvir/sofosbuvir with or without ribavirin, and 18 (3.4%) with sofosbuvir/ribavirin (Table 3).

Of the 522 patients, 503 patients (96.4%) completed the DAA treatment. The reason(s) for the loss of 19 patients to the follow-up during the treatment were not described in their medical records. The treatment duration was 12 weeks (*n*=465, 92.4%), 16 weeks (*n*=14, 2.8%), 20 weeks (*n*=3, 0.6%), and 24 weeks (*n*=21, 4.2%).

Among the 503 patients who completed DAA treatment, 33 (6.6%) developed serious adverse events with grade 3 or 4: hepatotoxicity (*n*=20), hyperglycemia (*n*=5), thrombocytopenia (*n*=4), anemia (*n*=3), and renal insufficiency (*n*=1), during the DAA treatment. These laboratory documented serious adverse events were observed more frequently in the patients who received the daclatasvir containing regimens than those without daclatasvir regimens (14.3%, 9/63 *vs.* 5.5%, 24/440; *P*=0.04), while the difference was not significant between the patients who received ribavirin-containing and non-containing regimens (6.3%, 30/478 *vs.* 12.0%, 3/25; *P*=0.26). Modifications of the DAA treatment due to these laboratory-documented serious adverse events were not required during the treatment period.

3.3. The SVR12 evaluation, outcomes of the DAA treatment, and further hospital visits

Only 315 out of the 503 patients who completed the DAA treatment (62.6%) returned to the hospital for SVR12 evaluation. Overall SVR12 was 98.7% regardless of HCV genotypes and DAA regimens. The SVR12 stratified by the infected HCV genotypes and DAA regimens is shown in Table 3.

Of the 123 patients with cirrhosis, 119 completed the DAA treatment (lost to the follow-up rate of 3.3%), 75 (63.0%) of the 119 patients who completed the treatment came back for SVR12 evaluation, and 30 patients (25.2%) returned for post-treatment follow-up. Among the 75 patients evaluated for SVR12, 74 (98.7%) reached SVR12. Of the 353 patients with non-cirrhosis, 343 completed the DAA treatment (lost to the follow-up rate of 2.8%),

Table 3. The treatment outcome of the 315 patients stratified by the HCV genotypes and the DAA regimens.

Regimens	HCV Genotype	N	n	SVR12, n (%) Yes	SVR12, n (%) No
Daclatasvir/sofosbuvir	1a	4	2	2 (100.0)	
	1b	1	1	1 (100.0)	
	1	1	1	1 (100.0)	
	6	1	1	1 (100.0)	
Daclatasvir/sofosbuvir/ ribavirin	1a	10	5	4 (80.0)	1 (20.0)
	1b	8	5	5 (100.0)	
	1	2	2	2 (100.0)	
	2	1	1	1 (100.0)	
	3	2	0		
	6	29	18	18 (100.0)	
	n.a.	4	2	2 (100.0)	
Ledipasvir/sofosbuvir	1a	3	2	2 (100.0)	
	1b	2	1	1 (100.0)	
	6	11	6	6 (100.0)	
	n.a.	2	2	2 (100.0)	
Ledipasvir/sofosbuvir/ ribavirin	1a	67	47	46 (97.9)	1 (2.1)
	1b	47	33	33 (100.0)	
	1	5	4	4 (100.0)	
	2	5	2	2 (100.0)	
	3	8	4	4 (100.0)	
	6	182	96	95 (99.0)	1 (1.0)
	1 and 3	1	0		
	n.a.	22	16	16 (100.0)	
Sofosbuvir/pegylated-interferon and ribavirin	1a	8	8	7 (87.5)	1 (12.5)
	1b	8	7	7 (100.0)	
	1	3	3	3 (100.0)	
	2	2	1	1 (100.0)	
	3	15	10	10 (100.0)	
	6	26	19	19 (100.0)	
	n.a.	6	6	6 (100.0)	
Sofosbuvir/ribavirin	1	1	1	1 (100.0)	
	2	8	4	4 (100.0)	
	3	6	3	3 (100.0)	
	6	1	1	1 (100.0)	
	n.a.	1	1	1 (100.0)	
Total		503	315	311 (98.7)	4 (1.3)

Among the 503 (*N*) who completed the DAA (direct-acting antivirals) treatment, 315 patients (*n*) were evaluated SVR12 (sustained virological response at 12 weeks after the end of DAA treatment). HCV; hepatitis C virus; n.a.: not available.

213 (62.1%) of the 343 patients who completed the treatment came back for SVR12 evaluation, and 57 (16.6%) returned for post-treatment follow-up. Among the 213 patients evaluated for SVR12, 210 (98.6%) reached SVR12. There was no significant difference in the lost to the follow-up rate, SVR12 evaluation rate, and SVR12 rate between the patients with and without cirrhosis.

Of the 503 who completed the treatment, 89 patients (17.7%) returned for post-treatment follow-up (Figure 1). Among the patients whose TE scores at baseline were available, the post-treatment follow-up rate was higher in the patients with cirrhosis (25.2% *vs.* 16.6%; *P*=0.04).

3.4. Changes in laboratory data after the DAA treatment

The liver function tests returned to normal ranges after the DAA treatment among patients of whom the data before and after treatment were available (Table 4). The median TE scores of the 101 patients, whose TE data were available at three points, significantly decreased from 10.2 kPa (IQR 6.8-16.9) before the treatment to 8.6 kPa (IQR 6.1-14.8) at the end of the treatment, and then to 6.3 kPa (IQR 4.9-11.7) at 12 weeks after the end of the treatment (P<0.001, Table 4). Comparing with the baseline data, the fibrosis stage was improved in 53 of the 101 patients, did not change in 38 patients, and got worse in 10 patients at 12 weeks after the end of the treatment.

4. Discussion

In the present study, the treatment outcome of generic DAA for Vietnamese CHC patients treated in 2016 were evaluated. The rate of SVR12 was as high as 98.7% regardless of HCV genotypes and DAA regimens with the attenuation of liver stiffness from 10.2 kPa before the treatment to 6.3 kPa at the 12 weeks after the end of DAA treatment. This is a study to describe the improvement of liver stiffness and the normalization of liver function tests in CHC patients after DAA treatment in the community in Vietnam.

Liver stiffness measured by a transient electrography is a surrogate marker of histological liver fibrosis[12,13] that is associated with the development of decompensated cirrhosis and hepatocellular carcinoma (HCC) as well as with mortality[14]. Several prospective studies demonstrated that the eradication of HCV reduced the progression rates of liver fibrosis and the risk of developing HCC[15–17]. In the present study, a significant reduction in liver stiffness and the normalization of liver function tests were observed in patients who achieved SVR12[18,19]. The result provides a strong rationale for the initiation of DAAs for all patients with CHC including those who have cirrhosis in Vietnam.

Nineteen out of the 522 patients (3.6%) were lost to the follow-up during the DAA treatment. Among the 503 patients who completed the DAA treatment, 62.6% returned to the hospital for the SVR12 evaluation, and only 17.7% were followed up after treatment period. Missing SVR12 evaluation and no further follow-up may increase the risk to miss relapse and re-infection of HCV infection. Regular screening for HCC is recommended as there is a risk to develop HCC even after the cure of HCV infection[3]. Previous studies reported that younger age, prison-based treatment, a history of mental health disease, active drug use, and type of insurance are factors related to being lost to the follow-up[20–22]. However, in the present study, the related factors were not sufficiently investigated, since it was conducted retrospectively. Further assessments are urgently needed to elucidate the reason(s) for being lost to the follow-up and missing the SVR12 evaluation and assessment of HCC development particularly in persons with cirrhosis in order to improve patient care for CHC in Vietnam.

As the rate of laboratory documented serious adverse events in

Table 4. The change of laboratory data of participants of whom all data at baseline and the other follow-up periods were available.

Indicators	n	Basiline (B)	At the end of treatment (EOT)	P value B vs. EOT	At 12 weeks after the EOT (12 W)	P value B vs. 12W
Hemoglobin, g/L	231	148 (139-158)	129 (117-142)	<0.001	154 (142-164)	<0.001
Platelet, ×10⁹/L	231	189 (145-237)	203 (156-258)	<0.001	191 (153-225)	
INR	139	1.03 (0.98-1.08)	1.01 (0.98-1.06)		1.00 (0.96-1.03)	<0.001
Glucose, μmol/L	220	5.1 (4.6-5.6)	5.0 (4.5-5.7)		5.2 (4.7-5.8)	
Creatinine, μmol/L	225	87 (77-98)	91 (79-102)	0.03	95 (83-105)	<0.001
T-Bil, μmol/L	182	12.9 (9.6-16.7)	12.8 (10.4-16.4)		11.1 (8.8-14.5)	<0.001
D-Bil, μmol/L	104	5.4 (3.3-7.6)	4.8 (3.2-7.0)		3.8 (2.7-5.3)	<0.001
Albumin, g/L	43	46 (43-48)	45 (42-48)		47 (45-50)	
AST, U/L	229	62 (38-104)	24 (19-31)	<0.001	24 (20-31)	<0.001
ALT, U/L	230	94 (52-163)	20 (14-30)	<0.001	21 (14-31)	<0.001
GGT, U/L	221	86 (51-163)	24 (16-47)	<0.001	26 (17-42)	<0.001
AFP, ng/mL	115	5.0 (2.8-12.7)	3.0 (2.0-5.1)	<0.001	3.0 (2.1-4.9)	<0.001
TSH, μU/mL	40	1.4 (1.1-2.6)	1.4 (1.1-2.3)		1.8 (1.0-2.6)	
FT4, pmol/L	40	15.7 (13.6-16.9)	15.4 (13.8-17.5)		15.5 (14.2-17.7)	
TE score, kPa	101	10.2 (6.8-16.9)	8.6 (6.1-14.8)		6.3 (4.9-11.7)	<0.001
F0 at the baseline	10	4.2 (3.8-4.6)	5 (4.1-6.4)		4.4 (3.6-5.2)	
F1 at the baseline	21	6.2 (5.7-6.8)	6.3 (5.3-8.0)		5.0 (4.5-5.8)	0.01
F2 at the baseline	15	7.8 (7.6-8.0)	6.5 (6.1-7.6)		5.3 (4.6-6.2)	0.02
F3 at the baseline	25	11.2 (10.3-12.3)	8.8 (7.2-11.1)	0.03	6.8 (6.0-9.8)	<0.001
F4 at the baseline	30	24.2 (17.7-29.6)	17.5 (14.7-27)	0.001	14.6 (11.5-19.9)	<0.001

Data were expressed as median (IQR). B: baseline; EOT: at the end of treatment; 12W: at 12 weeks after the EOT; IQR: interquartile range; INR: international normalized ratio; T-Bil: Total bilirubin; D-Bil: direct bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; AFP: alpha-fetoprotein; TSH: thyroid stimulating hormone; FT4: free thyroxine; TE: transient elastography. Friedman's test and *post hoc* with Bonferroni correction was applied to compare the values at the baseline and other follow-up periods; P<0.05 are shown.

daclatasvir containing regimen was higher than that in the other regimen groups in the current study, treating physician may need to take an appropriate awareness-raising measure for the patient treating with daclatasvir for proper patient care.

It is also important to note that the number of female patients who sought DAA treatment was less than that of males (female, n=132; male, n=390) and females were older (P<0.001) than males. These differences may be attributed to the difference in HCV prevalence and screening bias by gender or late attendance to a hospital because of the slow rate of disease progression in females[23–25]. Kanwal *et al*. revealed that young female patients with CHC were treated with DAA less frequently than male patients and suggested the necessity of targeted interventions for this population[26]. To address the factor(s) related to gender and age differences in CHC patients in the present study, a population survey on the prevalence of HCV and a risk factor analysis at the national level are needed to identify specific populations that need intensive interventions.

The present study had several limitations. It was conducted at one tertiary treatment hospital in northern Vietnam, which may be associated with a referral bias. Thus, the present results cannot be generalized to the whole area of Vietnam. Furthermore, this was a retrospective analysis and important information, such as treatment information for HIV and HBV infection, use of opioid therapy, ongoing drug use, level of alcohol consumption, and reasons for being lost to follow-up during treatment and missing the SVR12 evaluation, was not always documented properly in medical records, which may have resulted in underestimations. Alcohol use disorder is one of the risk factors for decompensated cirrhosis in CHC[27]. Alcohol dependence (5.9% in the male population) and injecting drug use are serious issues in Vietnam[28,29]. In addition, non-alcoholic fatty liver disease is a major factor associated with the persistent alternation of liver transaminases and liver stiffness after the achievement of a cure from HCV infection[30,31]. These risks, which may compromise the prognosis of patients with CHC were not assessed well in the present study. Further studies to address the incidence and risk of HCC development after the achievement of SVR are also needed in Vietnam.

In conclusion, the overall SVR12 with generic DAAs was sufficiently high regardless of HCV genotypes or DAA regimens with a high treatment completion rate in Vietnam. The liver stiffness significantly decreased after the DAA treatment. This study highlights the feasibility of implementing DAA treatment to cure all CHC patients at any level of liver fibrosis including cirrhosis in Vietnam as well as other low- and middle-income countries.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgements

Funding

Authors' contributions

HTTV and AI designed the study with input from HNN, HTL, and HI. QTN, HTTV, and AI were responsible for overall data collection with input from HNN. HTTV and AI conducted data analysis and interpretation. HTTV drafted the first manuscript. AI and HI revised the manuscript critically. All authors read and approved the final manuscript. KVN and HI supervised the project.

References

[1] World Health Organization. *Global hepatitis report 2017*. 2017. [Online]. Available from: https://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf?sequence=1. [Accessed on 6 August 2020].

[2] World Health Organization. *Global health sector strategy on viral hepatitis 2016–2021. Towards ending viral hepatitis*. 2016. [Online]. Available from: https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf?sequence=1. [Accessed on 6 August 2020].

[3] World Health Organization. *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection*. 2018. [Online]. Available from: https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1. [Accessed on 6 August 2020].

[4] Ishizaki A, Tran VT, Nguyen CH, Tanimoto T, Hoang HTT, Pham HV, et al. Discrepancies in prevalence trends for HIV, hepatitis B virus, and hepatitis C virus in Haiphong, Vietnam from 2007 to 2012. *PLoS One* 2017; **12**(6): e0179616.

[5] Berto A, Day J, Van Vinh Chau N, Thwaites GE, My NN, Baker S, et al. Current challenges and possible solutions to improve access to care and treatment for hepatitis C infection in Vietnam: A systematic review. *BMC Infect Dis* 2017; **17**(1): 260.

[6] Regional Office for the Western Pacific, World Health Organization. *Hepatitis data and statistics*. 2018. [Online]. Available from: https://www.who.int/westernpacific/health-topics/hepatitis/regional-hepatitis-data. [Accessed on 6 August 2020].

[7] The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling

study. *Lancet Gastroenterol Hepatol* 2017; **2**(3): 161-176.

[8] World Health Organization. *Global health estimates 2016: Deaths by cause, age, sex, by country and by region, 2000–2016.* 2018. [Online]. Available from: https://www.who.int/healthinfo/global_burden_disease/estimates/en/. [Accessed on 6 August 2020].

[9] World Health Organization. *Global report on access to hepatitis C treatment. Focus on overcoming barriers.* 2016. [Online]. Available from: https://apps.who.int/iris/bitstream/handle/10665/250625/WHO-HIV-2016.20-eng.pdf?sequence=1. [Accessed on 6 August 2020].

[10]Tanimoto T, Nguyen HC, Ishizaki A, Chung PT, Hoang TT, Nguyen VT, et al. Multiple routes of hepatitis C virus transmission among injection drug users in Hai Phong, Northern Vietnam. *J Med Virol* 2010; **82**(8): 1355-1363.

[11]Thi Thu Thuy P, Bunchorntavakul C, Dat HT, Palecki J, Reddy KR. Sofosbuvir-ledipasvir with or without ribavirin for chronic hepatitis C genotypes 1 and 6: Real-world experience in Vietnam. *Antivir Ther* 2018; **23**(5): 415-423.

[12]Enomoto M, Ikura Y, Tamori A, Kozuka R, Motoyama H, Kawamura E, et al. Short-term histological evaluations after achieving a sustained virologic response to direct-acting antiviral treatment for chronic hepatitis C. *United European Gastroenterol J* 2018; **6**(9): 1391-1400.

[13]Pan JJ, Bao F, Du E, Skillin C, Frenette CT, Waalen J, et al. Morphometry confirms fibrosis regression from sustained virologic response to direct-acting antivirals for hepatitis C. *Hepatol Commun* 2018; **2**(11): 1320-1330.

[14]Singh S, Fujii LL, Murad MH, Wang Z, Asrani SK, Ehman RL, et al. Liver stiffness is associated with risk of decompensation, liver cancer, and death in patients with chronic liver diseases: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2013; **11**(12): 1573-1584.

[15]Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol* 2018; **68**(1): 25-32.

[16]Romano A, Angeli P, Piovesan S, Noventa F, Anastassopoulos G, Chemello L, et al. Newly diagnosed hepatocellular carcinoma in patients with advanced hepatitis C treated with DAAs: A prospective population study. *J Hepatol* 2018; **69**(2): 345-352.

[17]Chen Yi Mei SLG, Thompson AJ, Christensen B, Cunningham G, McDonald L, Bell S, et al. Sustained virological response halts fibrosis progression: A long-term follow-up study of people with chronic hepatitis C infection. *PLoS One* 2017; **12**(10): e0185609.

[18]Singh S, Facciorusso A, Loomba R, Falck-Ytter YT. Magnitude and kinetics of decrease in liver stiffness after antiviral therapy in patients with chronic hepatitis C: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2018; **16**(1): 27-38.

[19]Lee YC, Hu TH, Hung CH, Lu SN, Chen CH, Wang JH. The change in liver stiffness, controlled attenuation parameter and fibrosis-4 index for chronic hepatitis C patients with direct-acting antivirals. *PLoS One* 2019; **14**(4): e0214323.

[20]Haridy J, Wigg A, Muller K, Ramachandran J, Tilley E, Waddell V, et al. Real-world outcomes of unrestricted direct-acting antiviral treatment for hepatitis C in Australia: The South Australian statewide experience. *J Viral Hepat* 2018; **25**(11): 1287-1297.

[21]Cachay ER, Hill L, Torriani F, Ballard C, Grelotti D, Aquino A, et al. Predictors of missed hepatitis C intake appointments and failure to establish hepatitis C care among patients living with HIV. *Open Forum Infect Dis* 2018; **5**(7): ofy173.

[22]Zuckerman A, Douglas A, Nwosu S, Choi L, Chastain C. Increasing success and evolving barriers in the hepatitis C cascade of care during the direct acting antiviral era. *PLoS One* 2018; **13**(6): e0199174.

[23]Backus LI, Belperio PS, Loomis TP, Mole LA. Impact of race/ethnicity and gender on HCV screening and prevalence among U.S. veterans in Department of Veterans Affairs Care. *Am J Public Health* 2014; **104**(Suppl 4): S555-S561.

[24]Bourgi K, Brar I, Baker-Genaw K. Health disparities in hepatitis C screening and linkage to care at an integrated health system in Southeast Michigan. *PLoS One* 2016; **11**(8): e0161241.

[25]Baden R, Rockstroh JK, Buti M. Natural history and management of hepatitis C: Does sex play a role? *J Infect Dis* 2014; **209**(Suppl 3): S81-S85.

[26]Kanwal F, Kramer JR, El-Serag HB, Frayne S, Clark J, Cao Y, et al. Race and gender differences in the use of direct acting antiviral agents for hepatitis C virus. *Clin Infect Dis* 2016; **63**(3): 291-299.

[27]Alavi M, Janjua NZ, Chong M, Grebely J, Aspinall EJ, Innes H, et al. The contribution of alcohol use disorder to decompensated cirrhosis among people with hepatitis C: An international study. *J Hepatol* 2018; **68**(3): 393-401.

[28]Go VF, Minh NL, Frangakis C, Ha TV, Latkin CA, Sripaipan T, et al. Decreased injecting is associated with increased alcohol consumption among injecting drug users in northern Vietnam. *Int J Drug Policy* 2013; **24**(4): 304-311.

[29]World Health Organization. *Global status report on alcohol and health 2018.* 2018. [Online]. Available from: https://apps.who.int/iris/bitstream/handle/10665/274603/9789241565639-eng.pdf?ua=1. [Accessed on 6 August 2020].

[30]Noureddin M, Wong MM, Todo T, Lu SC, Sanyal AJ, Mena EA. Fatty liver in hepatitis C patients post-sustained virological response with direct-acting antivirals. *World J Gastroenterol* 2018; **24**(11): 1269-1277.

[31]Olveira A, Domínguez L, Troya J, Arias A, Pulido F, Ryan P, et al. Persistently altered liver test results in hepatitis C patients after sustained virological response with direct-acting antivirals. *J Viral Hepat* 2018; **25**(7): 818-824.