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Incidence and predictors for abnormal liver function during direct-acting antiviral agents in chronic hepatitis C patients

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Abstract

Abrupt alanine aminotransferase (ALT) elevation during direct-acting antiviral agents (DAA) treatment is an uncommon but noticeable adverse event in chronic hepatitis C (CHC) patients, which may lead to early termination of treatment. This study aims to investigate the incidence, outcome and predictors of the on-treatment ALT elevation during DAA therapy.

CHC patients treated with DAA regimen in Chang Gung Memorial Hospital, Linkou branch during March 2015 to March 2019 were recruited. Prospective scheduled ALT assessment at baseline, 2nd, 4th, 8th, and 12th/24th weeks were recorded. Pretherapy host and viral factors were compared between patients with and without on-treatment ALT elevation. Multivariate logistic regression was used for independent factors for on-treatment ALT elevation.

A total of 1563 CHC patients treated with grazoprevir/elbasvir, glecaprevir/pibrentasvir and sofosbuvir-based regimen were analyzed. On-treatment ALT elevation occurred in 10.9% patients while those treated with glecaprevir/pibrentasvir had the least possibility (5.4%). Only 1.4% patients had ≥grade 3 ALT elevation events. The presence of such events had no impact on sustained virological response 12 rates. Hepatitis B virus coinfection (aOR: 3.599, $P < 0.001$) and higher pretherapy ALT (1-5x, ≥5x upper limit of normal: aOR: 2.632, $P = 0.024$, aOR: 4.702, $P = .011$, respectively) were significant predictors for ALT elevation.

On-treatment ALT elevation occurred in one-tenth CHC patients treated with preferred DAAs but had no impact on sustained virological response rate.

Abbreviations: AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ASV/DCV = asunaprevir + daclatasvir, BMI = body mass index, CHC = chronic hepatitis C, DAA = direct acting antiviral, G/E = grazoprevir/elbasvir, G/P = glecaprevir/pibrentasvir, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LFT = liver biochemistry, PrOD = ombitasvir/paritaprevir/ritonavir/dasabuvir, SVR = sustained virological response, T-bil. = total bilirubin, ULN = upper limit of normal.

Keywords: drug related hepatitis, glecaprevir/pibrentasvir, grazoprevir/elbasvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir

1. Introduction

Direct acting antiviral agents (DAAs) treatment greatly improved the sustained virological response (SVR) rate in chronic hepatitis C (CHC) patients from 70% by interferon-based regimen to >90%, with much less side effect and more tolerable in compensated and decompensated cirrhotic patients as well as the elderly.[1–5]

In 2015, severe liver injury and deterioration of liver function during ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekirax, PrOD) treatment has been reported in 26 CHC patients with advanced liver disease by the US Food and Drug Administration (FDA). Ten of the 26 patients had hepatic failure resulting in transplantation or death.[6] In 2019, warning of liver decompensation during the use of grazoprevir/elbasvir (Zepatier, G/E), glecaprevir/pibrentasvir (Maviret, G/P) and sofosbuvir/velpatasvir/voxilaprevir (Vosevi) was issued by FDA with the interval of 22 days from start of therapy.[7] High grade, especially grade ≥3, liver biochemistry (LFT) abnormalities during treatment leading to adverse events and early termination were also reported in clinical trials.[8–12]

Little is known about the incidence of on-treatment alanine aminotransferase (ALT) elevation in real-world practice as well as its impact on treatment outcome such as DAA discontinuation

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rate and SVR rate. Thus, this study aims to investigate the incidence, predictors and outcome of the on-treatment ALT elevation during DAA therapy in CHC patients.

2. Patients and methods

2.1. Patient selection

CHC patients, defined as persist anti- hepatitis C virus (HCV) antibody positive with viremia for more than 6 months, treated with interferon-free DAA regimen during March 2015 to March 2019 in Chang Gung Memorial Hospital, Linkou branch, Taiwan were prospectively registered with retrospective analyzed. This study was conducted adherence to the Declaration of Helsinki and approved by the Institutional review board (No. 1805240064) of Chang Gung Memorial Hospital. Patients older than 18-year-old with detectable HCV RNA at the time of antiviral therapy were eligible. Patients who did not complete the treatment course due to reasons other than abnormal LFT were excluded. Those with viable hepatocellular carcinoma (HCC) confirmed by ultrasound, CT scan or MRI within 3 months before screening were also excluded to avoid the cofounding effect on abnormal LFT secondary to HCC treatment.

2.2. Antiviral therapy

A 8 to 24 weeks course of DAA therapy was given depends on HCV genotype, liver fibrosis status, and DAA regimen chosen adherent to guideline suggestion.[13–15] Patients treated with preferred DAAs suggested by current guidelines including (Zepatier[Merck], G/E), (Maviret [AbbVie], G/P) and sofosbuvir-based regimens including sofosbuvir + ribavirin, sofosbuvir/velpatavir (Epclusa [Gilead]), and sofosbuvir/ledipasvir (Harvoni [Gilead]) were analyzed.

Additional 467 patients receiving ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekirax, PrOD, N=324) and asunaprevir/daclatasvir (ASV/DCV, N=143) were compared for the incidence and timing of "on-treatment ALT elevation" in the supplementary analysis.

2.3. Pretreatment characteristics and on-treatment monitoring and assessment

The pretreatment characteristics including age, sex, body mass index(BMI), steatosis, aspartate aminotransferase (AST), ALT, total bilirubin (T-bil.), albumin, international normalized ratio, alpha-fetoprotein (AFP), glycohemoglobin, total cholesterol, triglyceride, LDL, HDL, HOMA index, HCV genotype, HCV viral load and co-infected with hepatitis B virus were compared between patients with and without "on-treatment ALT elevation".

ALT and T-bil. level were prospectively assessed by scheduled timepoints: baseline, 2nd, 4th, 8th, and 12th/24th weeks during DAA treatment. "On-treatment ALT elevation" was defined as ALT elevation ≥1.1 times(x) baseline or nadir value accompanied by ALT elevation ≥1.25x the upper limit of normal (ULN) values.[16,17] "Abnormal total bilirubin" was defined as T-bil. elevation ≥1.5 times(x) baseline or nadir accompanied by ≥1.1x the ULN values.[16] The severity of ALT elevation was categorized by 1.25x-3x ULN as grade 1, >3x-5x ULN as grade 2, >5x-20x ULN as grade 3, and >20x ULN as grade 4. The severity of T-bil. elevation was categorized by 1.1x-1.5x ULN as grade 1, >1.5x-3x ULN as grade 2, >3x-10x ULN as grade 3, and >10x ULN as grade 4.[16] SVR was defined as undetectable HCV RNA at post DAA treatment week 12 (SVR12). Liver cirrhosis was diagnosed by histological findings (N=43), and/or consistent ultrasonographic features compatible with liver cirrhosis supplemented with splenomegaly and/or thrombocytopenia (N=762), and/or endoscopy finding with varices (N=151). Steatosis was identified by conventional ultrasonography.[18]

2.4. Statistical analysis

Continuous variables were summarized as means ± SD or median (range) and analyzed by Student's unpaired t test or Mann–Whitney U tests according to their normality distribution. Categorical variables were summarized using frequencies and analyzed the outcome by chi-squared or Fisher exact test. Logistic regression was applied to investigate independent predictors of on-treatment abnormal ALT. All analyses were 2-tailed tests based on a significance level of 0.05. The statistical analysis was conducted using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

3. Results

3.1. Patient cohort and clinical characteristics

A total of 1563 patients completing preferred DAA suggested by guidelines were enrolled into analysis [grazoprevir/elbasvir, N=373; sofosbuvir-based, N=967 (sofosbuvir ± ribavirin, N=275; sofosbuvir/ledipasvir, N=589; sofosbuvir/velpatasvir, N=103), glecaprevir/pibrentasvir, N=223]. There were 11 patients lost follow-up during therapy, 20 patients discontinued treatment due to other causes rather than LFT abnormality and 173 patients with viable HCC status (Fig. 1). Drug-drug interaction was surveyed and avoided as possible prior to the start of DAA therapy.

Among these 1563 patients, the mean age was 64.1, 649 (41.5%) were male, 784 (50.2%) were cirrhotic, 1305 (83.5%) were treatment naïve, 865 (55.3%) were HCV genotype 1, and 100 (6.4%) had hepatitis B virus (HBV) coinfection (Table 1). "On treatment ALT elevation" was documented in 170 patients (10.9%). SVR 12 was achieved in 98.2% patients by preferred DAAs (99.4% with G/E, 97.4% with sofosbuvir-based regimens and 99.6% with G/P, Table 2). The SVR 12 rate was comparable to the preferred DAAs in patients treated with PrOD (98.8%) but much lower in those treated with ASV/DCV (90.9%) (Supplemental Table 1, http://links.lww.com/MD/E769). None of these patients using preferred DAAs had hepatic failure or liver-related mortality secondary to on-treatment abnormal LFT events.

3.2. Characteristics between patients with and without "on treatment ALT elevation"

Comparing to those without "on-treatment ALT elevation", patients with cirrhosis (66.5% vs 48.2%, P<0.001), HBV coinfection (12.4% vs 5.7%, $P<.001$), higher BMI (median: 25.5 vs 24 kg/m^2, $P<.001$), HbA1c (median: 6.0 vs 5.8, $P=.002$), HOMA index (median: 2.8 vs 2.1, $P<.001$), triglyceride (median: 102 vs 90 mg/dL, $P=.002$), ALT (median: 93 vs 52 U/L, $P<.001$), AST (median: 86 vs 48 U/L, $P<.001$), AFP (median: 6 vs 4 ng/mL, $P<.001$), T-bil. (median: 0.8 vs 0.7 mg/dL, $P=.001$) and lower albumin level (median: 4.1 vs 4.2 g/dL, $P=.026$) at pretherapy were more frequent to have "on-treatment ALT elevation" (Table 1). The incidence of "on-treatment ALT elevation" was

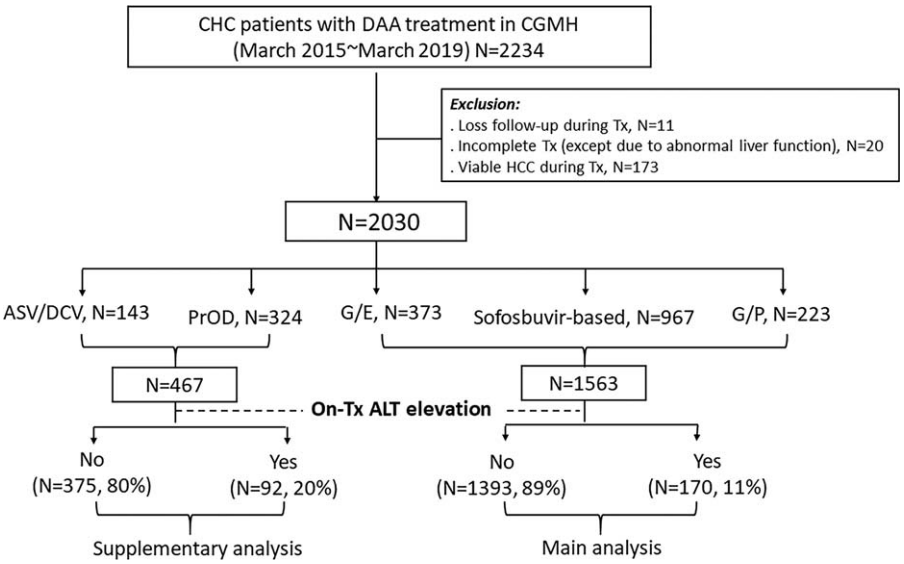

Figure 1. Study consort diagram with patients' recruitment.

Table 1

Pretherapy demographic comparison between patients with and without on-treatment ALT elevation.

Variables	All (N = 1563)	On-treatment ALT elevation		*P* value
		No (N = 1393, 89.1%)	Yes (N = 170, 10.9%)	
Age (yr)	64.1 ± 12.2	64.1 ± 12.4	64.5 ± 11.0	.663
Male, n (%)	649 (41.5)	582 (41.8)	67 (39.4)	.554
Cirrhosis, n (%)	784 (50.2)	671 (48.2)	113 (66.5)	<.001
Prior treatment, n (%)	258 (16.5)	228 (16.4)	30 (17.7)	.671
IFN, n (%)	254 (16.3)	225 (16.2)	29 (17.1)	.762
DAA	5 (0.3)	4 (0.3)	1 (0.6)	.438
Genotype, n (%)				
1	865 (55.3)	761 (54.6)	104 (61.2)	.103
Non-1	698 (44.7)	632 (45.4)	66 (38.8)	
HCV RNA (Log_{10}IU/mL)	6.2 (2.0–10.6)	6.2 (2.0–10.6)	6.2 (2.6–7.8)	.896
HBV coinfection, n (%)	100 (6.4)	79 (5.7)	21 (12.4)	<.001
BMI (kg/m^2)	24.1 (11.7–44.8)	24.0 (11.7–44.0)	25.5 (16.6–44.8)	<.001
HbA1c	5.8 (4.1–13.0)	5.8 (4.1–13.0)	6.0 (4.3–11.3)	.002
HOMA index	2.2 (0.2–84.1)	2.1 (0.2–84.1)	2.8 (0.6–74.4)	<.001
Cholesterol (mg/dL)	166 (63–317)	167 (84–317)	165 (63–311)	.796
Triglyceride (mg/dL)	91 (22–1119)	90 (22–442)	102 (33–1119)	.002
LDL (mg/dL)	97 (16–400)	97 (16–400)	97 (31–400)	.549
Steatosis, n (%)	436 (28.3)	378 (27.6)	58 (34.1)	.074
DAA, n (%)				.016
G/E	373 (23.9)	327 (23.5)	46 (27.1)	
Sofosbuvir-based	967 (61.8)	855 (61.4)	112 (65.9)	
G/P	223 (14.3)	211 (15.1)	12 (7.0)	
ALT (U/L)	55 (5–895)	52 (5–895)	93 (14–592)	<.001
<1xULN, n (%)	467 (29.9)	450 (32.3)	17 (10.0)	<.001
1–5x	972 (62.2)	849 (61.0)	123 (72.4)	
≥5x	124 (7.9)	94 (6.7)	30 (17.6)	
AST (U/L)	50 (11–622)	48 (11–622)	86 (15–440)	<.001
T-bil. (mg/dL)	0.7 (0.1–7.7)	0.7 (0.1–7.7)	0.8 (0.2–4.2)	.001
Albumin (g/dL)	4.2 (1.9–5.2)	4.2 (1.9–5.2)	4.1 (2.9–5.0)	.026
INR	1.1 (0.9–3.0)	1.1 (0.9–3.0)	1.1 (0.9–1.7)	<.001
AFP (ng/mL)	4 (1–4183)	4 (2–1558)	6 (1–4183)	<.001
Platelet (10^3/uL)	167 (15–574)	168 (15–574)	157 (30–349)	.085

AFP = alpha-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DAA = direct antiviral agents; G/E = grazoprevir/elbasvir; G/P = glecaprevir/pibrentasvir; HbA1c = glycohemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; IFN = interferon; INR = international normalized ratio; T-bil.: total bilirubin; ULN = upper limit of normal; x = times.

Table 2

SVR rate comparison between patients with and without on-treatment ALT elevation.

	G/E (N = 373)		Sofosbuvir-base (N = 967)		G/P (N = 223)	
	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal
No.	46 (12.3%)	327 (87.7%)	112 (11.6%)	855 (88.4%)	12 (5.4%)	211 (94.6%)
SVR*	45/46 (97.8%)	325/326 (99.7%)	107/111 (96.4%)	826/847 (97.5%)	12/12 (100%)	208/209 (99.5%)
P value	0.232		0.520		1.000	
Overall SVR*	370/372 (99.4%)		933/958 (97.4%)		220/221 (99.6%)	

* Twelve patients lost follow-up before the assessment of SVR12 after complete treatment.

G/E = Grazoprevir/Elbasvir; G/P = Glecaprevir/Pibrentasvir; SVR = sustained virological response.

slightly higher in patients with pretherapy steatosis (34.1% vs 27.6%, $P = .074$) yet not reach statistical difference. Among patients co-infected with HBV, there's no difference of "on-treatment ALT elevation" rate between the 3 different DAA regimens ($P = .737$).

3.3. Incidence of abnormal LFT during different DAA regimens

The frequency of "on-treatment ALT elevation" was highest in those treated with G/E (12.3%), followed by sofosbuvir-based regimen (11.6%) and least in G/P (5.4%) treated patients (P = 0.016) (Table 1), similar to those treated with PrOD (10.8%) but much lower than that during ASV/DCV (39.9%) (Supplemental Table 2, http://links.lww.com/MD/E770). The median time to event from start of treatment was shorter in those treated with G/P and PrOD (4 weeks), followed by sofosbuvir-based (6 weeks), G/E (7 weeks) and longest in those by ASV/DCV (12 weeks) (Table 3, Fig. 2). None of the G/P patients had ALT elevation severity ≥grade 3 while 7%, 3.2%, 1.9% and 1% in ASV/DCV, G/E, PrOD, and sofosbuvir treated patients had ALT elevation ≥grade 3 respectively (Table 3; Supplemental Table 2, http://links.lww.com/MD/E770).

The events of T-bil. elevation were observed in 13.2% patients treated with preferred DAA, highest in those treated by sofosbuvir-based regimen (16.4%) followed by G/P (8.5%) and G/E (7.8%), and much lower than those treated with ASV/DCV (23.1%) and PrOD (29.4%). Grade 3/4 abnormality occurred mainly in patients with PrOD (2.5%), followed by sofosbuvir-based (1.2%), G/P (0.9%), ASV/DCV (0.7%) and none with G/E.

3.4. Outcomes and treatment efficacy in patients encountering on-treatment ALT elevation

The SVR12 rates between patients with and without on-treatment ALT elevation was significantly different in those receiving ASV/DCV (83.9%: 95.4%. $P = .034$) and borderline significant in those with PrOD (94.3% vs 99.3%, $P = .059$). However, it has no impact on SVR 12 in patients treated with G/E ($P = .232$), sofosbuvir ($P = .520$), and G/P ($P = 1.000$) (Table 2; Supplemental Table 1, http://links.lww.com/MD/E769). One patient (0.27%) treated by G/E, 2 patients (1.4%) by ASV/DCV and 6 patients (1.8%) by PrOD regimens had early termination of DAA treatment due to abnormal liver function. Among these 9 patients, only 1 patient treated with PrOD had hepatic decompensation. The SVR12 rate in these 9 early treatment termination patients was much lower than those completing treatment (67%) (Table 3; Supplemental Table 2, http://links.lww.com/MD/E770). These patients' characteristics were listed as Supplemental Table 3, http://links.lww.com/MD/E771.

Table 3

The onset timing and severity of abnormal liver biochemistry during G/E, Sofosbuvir based and G/P therapy.

DAA	G/E (N = 373)	Sofosbuvir-based (N = 967)	G/P (N = 223)
Abnormal ALT, n (%)	46 (12.3)	112 (11.6)	12 (5.4)
Time to abnormal ALT (weeks)	7 (1–12)	6 (1–16)	4 (2–8)
0–2 (weeks), n (%)	1 (2.2)	4 (3.6)	1 (8.3)
2–4	6 (13.0)	25 (22.3)	3 (25.0)
4–8	16 (34.8)	47 (42.0)	5 (41.7)
≥ 8	23 (50.0)	36 (32.1)	3 (25.0)
ALT level (peak), n			
Grade 1	28	85	11
Grade 2	6	17	1
Grade 3	9	9	0
Grade 4	3	1	0
Abnormal T-bil., n (%)	29 (7.8)	159 (16.4)	19 (8.5)
T-bil. level (peak), n (%)			
Grade 1	18	68	4
Grade 2	11	79	13
Grade 3	0	12	2
Grade 4	0	0	0
Early termination due to abnormal LFT, n (%)	1 (0.27)	0	0

ALT = alanine aminotransferase; DAA = direct antiviral agents; G/E = grazoprevir/elbasvir; G/P = glecaprevir/pibrentasvir; LFT = liver biochemistry; SVR = sustained virological response; T-bil. = total bilirubin.

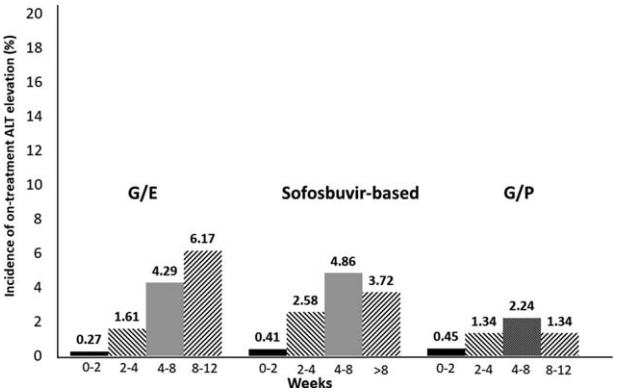

Figure 2. "On-treatment ALT elevation" events (%) and time of onset during grazoprevir/elbasvir, sofosbuvir-based, and glecaprevir/pibrentasvir treatment.

Table 4

Predictors of on-treatment ALT elevation in patients treated with G/E, sofosbuvir-based and G/P regimens.

Variables	Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value
Cirrhosis	2.133 (1.525–2.983)	<.001	1.735 (0.979–3.077)	.059
HBV coinfection	2.330 (1.399–3.881)	.001	3.599 (1.781–7.272)	<.001
BMI				
<25	Referent			
≥25	1.808 (1.309–2.497)	<.001	1.281 (0.779–2.105)	.329
HbA1c				
<6.5	Referent			
≥6.5	1.613 (1.087–2.394)	.018	1.582 (0.916–2.733)	.100
HOMA index				
<2	Referent			
≥2	1.985 (1.240–3.176)	.004	1.396 (0.811–2.402)	.228
Triglyceride				
<150	Referent			
≥150	1.658 (1.055–2.606)	.028	1.298 (0.688–2.450)	.420
DAA regimen				
G/P	Referent			
Sofosbuvir-based	2.303 (1.246–4.256)	.008	2.186 (0.750–6.373)	.152
G/E	2.473 (1.280–4.778)	.007	2.854 (0.928–8.772)	.067
ALT				
<1xULN	Referent			
1–5x	3.835 (2.280–6.450)	<.001	2.632 (1.135–6.104)	.024
≥5x	8.448 (4.476–15.944)	<.001	4.702 (1.424–15.530)	.011
AST	1.006 (1.004–1.009)	<.001	1.002 (0.997–1.007)	.450
INR	2.596 (1.059–6.365)	.037	1.372 (0.311–6.055)	.676
Total bilirubin	1.422 (1.113–1.817)	.005	0.964 (0.641–1.449)	.859
Albumin	0.764 (0.544–1.074)	.121	1.116 (0.625–2.176)	.629
AFP	1.001 (1.000–1.003)	.114		

AFP = alpha-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; G/E = grazoprevir/elbasvir; G/P = glecaprevir/pibrentasvir; HbA1c = glycohemoglobin; HBV = hepatitis B virus; INR = international normalized ratio; ULN = upper limit of normal; x = times.

3.5. Predictive factors for on-treatment ALT elevation

Among patients treated with preferred DAAs, cirrhosis, HBV coinfection, BMI ≥25, HbA1c ≥6.5, HOMA index ≥2, triglyceride≥150 mg/dL, use of sofosbuvir-based or G/E regimens, pretherapy ALT ≥1xULN, higher AST, AFP, T-bil. and lower albumin level were associated with on-treatment ALT elevation. In multivariate regression analysis, HBV coinfection [adjusted OR (95%CI): 3.599 (1.781–7.272), $P < .001$] and higher baseline ALT [ALT 1–5x, ≥5x ULN, adjusted OR (95% CI): 2.632 (1.135–6.104), $P = .024$; 4.702 (1.424–15.530), $P = .011$, respectively] were the independent predictor for on-treatment ALT elevation (Table 4). In addition, higher baseline ALT level is the only independent factors for on-treatment ALT elevation when excluding the patients with HBV coinfection (Supplemental Table 4, http://links.lww.com/MD/E772 and Supplemental Table 5, http://links.lww.com/MD/E773).

4. Discussion

In this large-scale real-world study, we reported the incidence rate of on-treatment ALT elevation and ≥grade 3 ALT elevation was 10.9% and 1.4%, respectively under currently recommended DAAs. Higher pretherapy ALT and HBV coinfection were the risk factor for on-treatment ALT elevation during preferred DAAs treatment, which has no impact on SVR rates and only 1 patient had early terminated treatment but still achieved SVR. To our knowledge, this is first real-world study addressing not only the incidence but time of onset, predictors and clinical impact of on-treatment ALT elevation among different DAAs.

The presence of abnormal LFT during DAA treatment may majorly owe to drug related events. It has been reported that drugs targeting the NS3/4 protease inhibitors may cause "on-treatment ALT elevation". The incidence was higher in patients treated with ASV/DCV (17.8%) but lower with PrOD (<1.2%).[19,20] The incidence of ALT elevation ≥grade 3 during ASV/DCV and G/P treatment in current study was mostly compatible with previous reports (ASV/DCV: 6.7% vs. 8.9%[19] and G/P: 0% vs. 0%[21,22]). However, higher proportion of "on-treatment ALT elevation" was observed in patients treated with PrOD and G/E in current cohort compared to prior studies (PrOD: 1.2% vs 0.5%,[23] G/E: 2.4% vs 0.9%[10]). This phenomenon may be resulted from much higher cirrhotic patients' proportion in our study comparing to others'. Although sofosbuvir, mainly blocking hepatitis C NS5B protein, was rarely reported with "on-treatment ALT elevation" events, there was still 1.6% of the 126 genotype 3 and 6 CHC patients reported with ≥grade 3 ALT elevation in a phase 2 trial treated with sofosbuvir/ledipasvir.[24] In our cohort which composed majorly genotype 1 and 2/3 CHC patients, there was 1% of 967 patients treated with sofosbuvir-based regimen observed with ≥grade 3 "on-treatment ALT elevation". Patients with higher pretherapy HbA1c, co-infection with HBV and higher pretherapy ALT level have higher probability to encounter "on-treatment ALT elevation" during sofosbuvir-based therapy (Supplemental Table 6, http://links.lww.com/MD/E831).

In this study, the median time to "on-treatment ALT elevation" was earlier in PrOD and G/P (4 weeks), followed by sofosbuvir-based, GE and latest in ASV/DCV (12 weeks). About 40% and 33.3% of the event took place within the 1st month in PrOD and

G/P treated patients respectively, while 74.1%, 84.8% and 94.7% of the event occurred after the 4th week in sofosbuvir-based, G/E and ASV/DCV treated cases. The reported incidence rate of ≥grade 3 T-bil. elevation during treatment was 0.9%, 4%, 4%, 0.3%, and 0.3% to 0.6% in ASV/DCV, PrOD, sofosbuvir-based, G/E and G/P, respectively,[9,10,19,22,25,26] which is comparable as 0.7%, 2.5%, 1.2%, 0, and 0.9% in the corresponding regimens in current study.

Serum albumin levels was reported as a factor associated with severe ALT elevations in ASV/DCV treated patients.[27] In our study, pretherapy ALT rather than albumin level was the only independent factor associated with on-treatment ALT elevation. With regard to HBV coinfected patients, the risk of HBV reactivation in patients treated with DAA has been reported, and most patients had asymptomatic increases of HBV DNA with or without ALT elevation.[28,29] Although patients with the presence of ultrasonography steatosis are prone to encounter "on-treatment ALT elevation" in overall cohort (34.1% vs 27.6%, $P=.074$) and in those without HBV co-infection (35.6% vs 28.2%, $P=.059$), yet not reach statistically significant difference especially after multivariate adjustment. The "on-treatment ALT elevation" occurred in 21 of the 100 HBV co-infected CHC patients receiving G/E, sofosbuvir-based and G/P therapy in current study, similar to the reactivation rate of 24% from a recent systemic review and meta-analysis.[30]

Notably, the abrupt ALT abnormality was not lasting in majority of cases, and only 0.06% of the preferred DAAs, 1.8% of PrOD and 1.4% of ASV/DCV treated patient terminated the treatment due to physician's concern but none liver-related mortality occurred. The SVR rate in our cohort was comparable to that reported in clinical trials (90.9% vs 90%, 98.8% vs 98%, 97.4% vs 97%, 99.4% vs 95% and 99.6% vs 99% in ASV/DCV, PrOD, sofosbuvir-based, G/E and G/P respectively).[9,10,21,25,31] The presence of ALT elevation did not influence the SVR rate in current preferred DAAs treated patients but lowered the SVR rate in ASV/DCV and PrOD treated patients to 83.9% ($P=.034$) and 94.3% ($P=.059$), respectively. This phenomenon was not mentioned in previous studies discussing the SVR factors in ASV/DCV treated patients. Moreover, the SVR rates was much lower as 67% in the 9 early termination patients due to abnormal liver function. From this result, patients who had abnormal LFT during preferred DAAs treatment without sign of hepatic decompensation shall complete their treatment instead of early termination.

Although this is a prospective registered retrospective analysis study, there are several limitations: First, in spite of the pretherapy survey and avoidance of possible drug-drug interaction, the details of co-medication of these abnormal LFT patients at the onset of "on-treatment ALT elevation" are not complete from retrospective medical record; Second, the amount of alcohol consumption was not prospectively recorded in our cohort and difficult to assess its impact by retrospective analysis; Third, not all the HBV co-infection patients had pretherapy HBV DNA level which difficult to assess the exact proportion of HBV reactivation related to "on-treatment ALT elevation"; Fourth, this is a clinical study lacking the experimental investigation on the mechanisms how this abnormal LFT occurs.

In conclusion, on-treatment ALT elevation is not rare event and may take place in 10.9% during G/E, Sofosbuvir and G/P treated patients. Only 1.4% patients had ≥grade 3 ALT elevation events. Since such events did not lead to hepatic decompensation nor influence on SVR rates. Patients encountering abnormal LFT elevation during these 3 DAA regimens may not need to terminate the treatment early but complete the antiviral therapy as scheduled.

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