Rapid platelet count improvement in chronic hepatitis C patients with thrombocytopenia receiving direct-acting antiviral agents

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Abstract
The effect of direct-acting antiviral agents (DAAs) on short-term platelet improvement in chronic hepatitis C (CHC) patients with thrombocytopenia is unclear.

From December 2015 to March 2018, a total of 249 CHC patients receiving DAA treatment with baseline thrombocytopenia (platelet count < 150 × 10^3/μL) at Dalin Tzu Chi Hospital were enrolled in this retrospective study. Blood examinations were conducted at baseline (BL), week 4 (W4) after DAA initiation, end of treatment (EOT), and 12 weeks after EOT (P12).

Hepatitis C virus (HCV) genotyping revealed that 184 patients (73.9%) carried HCV genotype 1. Of the patients in the cohort, 87 (34.9%) were interferon (IFN)-experienced, and 213 (85.5%) had advanced fibrosis status. All but 1 patient achieved SVR12 (sustained virologic response (SVR) rate, 99.6%; 248/249). The platelet count recovered significantly at all time points (P12 vs BL, P < .001; EOT vs BL, P < .001; P12 vs BL, P < .001). Multivariate analyses revealed moderate or severe fatty liver (P = .024) and lower baseline platelet count (P = .005) was significantly associated with platelet count improvement.

In conclusion, thrombocytopenia associated with CHC rapidly improves with the administration of DAA. Moderate or severe fatty liver and lower baseline platelet count predict significant improvement of platelet count.

Abbreviations: AFP = alpha-fetoprotein, ALT = alanine aminotransferase, APRI = aspartate aminotransferase to platelet ratio index, AST = aspartate aminotransferase, BL = baseline, BMI = body mass index, CHC = chronic hepatitis C, CI = confidence interval, DAA = direct-acting antiviral agent, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, EOT = end of treatment, FIB-4 = fibrosis-4, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IFN = interferon, OR = odds ratio, PAIg = platelet-associated immunoglobulin, RVR = rapid virologic response, SD = standard deviation, SVR = sustained virologic response, TPO = thrombopoietin, W4 = week 4.

Keywords: direct-acting antiviral agents, hepatitis C, sustained virologic response, thrombocytopenia

1. Introduction
Hepatitis C virus (HCV) infection not only affects liver function but also has extrahepatic manifestations, such as mixed cryoglobulinemia, glomerulonephritis, non-Hodgkin’s lymphoma, type 2 diabetes mellitus (DM), stroke, and cardiovascular diseases.[1,2] The achievement of a sustained virologic response (SVR) after interferon (IFN)-based therapy or direct-acting antiviral agent (DAA) improves liver fibrosis status[2,3] and several extrahepatic manifestations of HCV infection.[1,2] Thrombocytopenia is relatively common among HCV patients...
with chronic liver disease. The reported prevalence of thrombocytopenia in chronic hepatitis C (CHC) patients ranges from 0.16% to 45.4%, with most studies reporting a prevalence >20%. The pathophysiology of thrombocytopenia includes splenomegaly-related hypersplenism, impaired production of thrombopoietin (TPO) due to advanced liver fibrosis, autoantibody responses, and possible direct effect by HCV.

Several studies have shown that the platelet counts of CHC patients are improved in long-term follow-up after successful IFN-based therapy, but not in those without SVR, decreased platelet counts are reported for non-responders and never-treated CHC patients. The effect of DAA on the improvement of platelet counts is unknown. Treatment with sofosbuvir plus daclatasvir or ledipasvir has been shown to improve platelet counts after HCV eradication. Two short reports also supported that HCV treatment by DAA improves platelet counts after long-term follow-up. While 1 case report describes the exacerbation of thrombocytopenia after DAA treatment, this adverse effect is uncommon. The short-term effects of DAA on platelet counts and the predictive factors for platelet count improvement have not been well reported. Hence, this study investigates the effect of HCV eradication on platelet count during and after DAA treatment.

2. Patients and methods

2.1. Patient selection

Patients with CHC infection who underwent DAA treatment at Dalin Tzu Chi Hospital from December 2015 to March 2018 were enrolled in this retrospective study. All patients had been positive for anti-hepatitis C antibody for more than 6 months and had detectable serum levels of HCV RNA at the time of entry into the study. Treatment duration and regimen were based on guidelines. Patients with incomplete treatment course, incomplete medical records, or loss of post-treatment follow-up were excluded. A total of 469 patients were screened, and 249 patients with thrombocytopenia (platelet < 150 x 10^3/µL) were enrolled (Fig. 1). This study was approved by the Ethics Committee of Dalin Tzu Chi General Hospital (B10502022).

2.2. Clinical monitoring

For all patients, liver function tests (serum aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, creatinine, hemoglobin, white blood cell count, and platelets) and abdominal sonography were conducted at the hepatitis-gastrointestinal outpatient clinic at baseline (BL), week 4 (W4) after DAA initiation, end of treatment (EOT), and 12 weeks after EOT (P12). HCV RNA was quantified at BL, EOT, and P12. Liver cirrhosis and associated complications were evaluated every 3 to 6 months after initial diagnosis. Liver fibrosis was evaluated using the noninvasive fibrosis-4 (FIB-4) test. Advanced fibrosis was diagnosed as indicated by radiologic cirrhosis or FIB-4 > 3.25. Radiologic cirrhosis was defined as coarse liver echotexture with nodularity and small liver size or the presence of portal hypertension features (ascites, splenomegaly, and varicis) noted on liver imaging. Splenomegaly was diagnosed when the spleen length was more than 11 cm. A diagnosis of fatty liver was based on results from abdominal ultrasound that included hepatorenal echogenicity contrast, liver brightness, deep attenuation, and vessel blurring. All ultrasonographic images were stored as photographs. Other clinical factors, including diabetes mellitus, hypertension, chronic hepatitis B, hepatocellular carcinoma (HCC), and alcoholism, were recorded by chart review. Alcoholism was defined as alcohol consumption of more than 40 g/day. HCC was diagnosed either by biopsy or by imaging in the setting of liver cirrhosis. Chronic hepatitis B was diagnosed if a patient had seropositivity for hepatitis B surface antigen for at least 6 months. Significant platelet improvement was defined as a platelet count increase by more than 10% of the baseline count. Among these thrombocytopenic patients, we defined a cut-off value of 100 x 10^3/µL to differentiate high or low platelet counts.

2.3. HCV quantification and genotyping

Serum HCV RNA was quantified at BL, EOT, and P12 using the COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0 (Roche Diagnostics, Rotkreuz, Switzerland), with a lower limit of quantification of 15 IU/mL. HCV genotyping was performed using the COBAS HCV GT (Roche Diagnostics). The threshold to distinguish low from high baseline HCV RNA load was 400,000 IU/mL.

2.4. Sustained virologic response

SVR was defined as undetectable HCV RNA at P12. Patients who were positive for HCV RNA at P12 were considered non-SVR.

2.5. DAA regimens

The DAA regimens include ledipasvir/sofosbuvir, sofosbuvir/daclatasvir, sofosbuvir/ribavirin, sofosbuvir/velpatasvir, asunaprevir/daclatasvir, elbasvir/grazoprevir, and paritaprevir/ritonavir/ombitasvir with dasabuvir. These DAAAs were administered according to recommended guidelines.

2.6. Statistical analysis

SPSS 19.0 for Windows (SPSS Inc, Chicago, IL) was used for all statistical analyses. The mean and standard deviation (SD) for continuous variables and values for demographic and baseline clinical features are presented for all included patients. Demographics and baseline clinical features were compared between patients with and without significant platelet improvement. The chi-square test or Fisher’s exact test was used for nominal variables. Continuous variables were compared using Student’s t test for 2 independent groups. To identify factors associated with platelet improvement, multivariate logistic regression analyses were performed for the variables that were potentially significant (P < .1) in univariate analysis. Results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). P < .05 was considered significant in all analyses.

3. Results

3.1. Demographic and clinical characteristics, virologic response, and the improvement of platelet

A total of 249 thrombocytopenic CHC patients receiving DAA and followed up for 12 weeks after EOT were included for analysis. HCV genotyping revealed that 184 patients (73.9%) carried HCV genotype 1. Of the patients in the cohort, 174 (69.9%) had high viral load, 87 (34.9%) were IFN-experienced, and 213 (85.5%) had advanced fibrosis. A rapid virologic
response by W4 was achieved in all but 14 patients (rapid virologic response (RVR) rate, 94.4%; 235/249), and only 1 patient did not achieve SVR12 (SVR rate, 99.6%). The platelet count recovered significantly in 104 patients (41.7%; 104/249).

Baseline characteristics and clinical and laboratory data are shown in Table 1.

The mean platelet count of all thrombocytopenic patients is shown in Figure 2. For all thrombocytopenic patients, the mean baseline platelet count was 102 × 10^3/μL before DAA, increasing to 116 × 10^3/μL, 114 × 10^3/μL, and 113 × 10^3/μL at W4, EOT, and P12, respectively. Comparison of the mean platelet count at baseline with that at W4, EOT, and P12 showed statistically significant increases at all time points (W4 vs BL, P < .001; EOT vs BL, P < .001; P12 vs BL, P < .001).

3.2. Factors associated with significant platelet count improvement

Univariate analysis showed that moderate or severe fatty liver (P = .03), alpha-fetoprotein (AFP) (P = .049), and baseline platelet count (P = .045) were statistically significant with platelet count improvement. Multivariate analysis revealed moderate or severe fatty liver (odds ratio (OR), 2.918; P = .024) and baseline platelet count (OR, 0.987; P = .005), was significantly associated with platelet count improvement (Table 2).

Further analysis of factors significantly associated with platelet count improvement showed that CHC patients with moderate or severe fatty liver experienced significant improvement in platelet count at P12 as compared to patients without (P = .014) (Fig. 3a). CHC patients with lower baseline platelet count had significant improvement at EOT and P12 as compared to those with higher baseline platelet count (EOT, P = .039; P12, P = .03) (Fig. 3b).

4. Discussion

We observed that DAA therapy significantly increased the platelet counts of patients with CHC as early as 4 weeks after treatment. This increase persisted at P12. For those CHC patients with moderate or severe fatty liver, the improvement in platelet count was more prominent at P12 than in those without moderate or severe fatty liver. In addition, the baseline platelet count predicted the significant improvement at EOT and P12.

Several studies have investigated the relationship between HCV and platelet count after IFN treatment. However, IFN exacerbates thrombocytopenia because of its side effects, making the evaluation of platelet improvement during HCV treatment difficult. Severe thrombocytopenia occurred in 6.1% to 41.1% of CHC patients receiving IFN-based therapy. After successful IFN therapy, several long-term follow-up studies show significant increases in platelet counts. Decreased portal pressure is
thought to be a possible mechanism accounting for this IFN-induced increase in platelet count.[14,15] We observed that with DAA treatment, platelet counts increased rapidly at W4. This effect is less likely to be caused by prominent improvement in liver fibrosis at such a short time after DAA treatment[2] and likely involves other mechanisms. Several other studies also report platelet improvement after DAA treatment.[18–21] Welzel et al observed that the platelet counts of CHC patients taking daclatasvir plus sofosbuvir and increased by 7.0 × 10^9/L from baseline to week 12 after completion of a DAA course.[18] Rafei et al reported that ledipasvir plus sofosbuvir treatment increased platelet counts. However, this study only investigated 1 type of DAA. In addition, the duration of DAA treatment and the timing of platelet counts assessment varied. Therefore, only the overall increasing trend in platelet count is valid for comparison.[19] Our study demonstrates a clear platelet improvement response to DAA treatment, platelet counts increased rapidly at W4. This long-term effect may be related to the improvement in liver fibrosis.

Mechanisms involved in the pathophysiology of thrombocytopenia, including direct effects of the virus, anti-GPIIb-IIIa antibodies, and antiplatelet antibodies may underlie the rapid improvement of platelet count we observed after DAA treatment. Dai et al and de Almeida et al showed that HCV itself might be partly responsible for cirrhotic thrombocytopenia and that patients with HCV-related cirrhosis were more likely to have anti-GPIIb-IIIa antibody-producing B cells than those with HBV-related cirrhosis.[32] There-fore, the improvement of platelet count after the eradication of HCV is expected. Kajihara et al evaluated anti-GPIIb antibodies in cirrhotic patients and found these autoantibodies may be partly responsible for cirrhotic thrombocytopenia and that patients with HCV-related cirrhosis were more likely to have anti-GPIIb-IIIa antibody-producing B cells than those with HBV- or alcohol-related cirrhosis.[10] Aref et al also demonstrated the presence of antiplatelet antibodies in CHC patients, with platelet-associated immunoglobulin (PAIg) present in thrombocytopenic CHC patients. This study did not investigate autoantibodies so comparison is not possible. While HCV eradication would not rapidly reverse liver fibrosis, it could decrease the “antigen” (HCV) such that the autoantibody production would decrease as well. Our study indirectly supports the theory that HCV induces antiplatelet antibody or that HCV itself affects the platelet lifespan. Clarification of this issue requires further study.

Moderate or severe fatty liver was significantly associated with improvement of platelet count after DAA treatment in our study. The platelet counts of our CHC patients with fatty liver

Table 1
Baseline characteristics and laboratory data of chronic hepatitis C patients with thrombocytopenia according to platelet improvement status.

|                       | All patients (n = 249) | With significant platelet improvement (n = 104) | Without significant platelet improvement (n = 145) | P     |
|-----------------------|------------------------|-----------------------------------------------|--------------------------------------------------|-------|
| Age (y)†              | 68.1 ± 10.9            | 67.9 ± 10.3                                   | 68.2 ± 11.4                                       | .827  |
| BMI (kg/m²)†          | 25.3 ± 4.3             | 25.5 ± 4.7                                    | 25.1 ± 4.1                                       | .643  |
| Male (%)              | 102 (41.0)             | 45 (43.3)                                     | 57 (39.3)                                        | .531  |
| DM (%)                | 51 (20.5)              | 23 (22.1)                                     | 28 (19.3)                                        | .589  |
| Hypertension (%)      | 57 (22.9)              | 20 (19.2)                                     | 37 (25.5)                                        | .244  |
| Hyperlipidemia (%)    | 9 (3.6)                | 3 (3.2)                                       | 6 (4.1)                                          | .601  |
| Alcoholism (%)        | 21 (8.4)               | 13 (12.5)                                     | 8 (5.9)                                          | .051  |
| Moderate or severe fatty liver (%) | 24 (9.6)     | 15 (14.1)                                     | 9 (6.2)                                          | .020  |
| ALT (U/L)             | 102.6 ± 79.4           | 97.7 ± 74.1                                   | 106.1 ± 93.0                                     | .412  |
| AST (U/L)             | 80.5 ± 66.4            | 72.3 ± 55.0                                   | 86.5 ± 73.2                                       | .096  |
| Albumin (g/dL)†       | 3.99 ± 0.43            | 4.01 ± 0.40                                   | 3.97 ± 0.45                                       | .486  |
| Total bilirubin (mg/dL)† | 0.96 ± 0.48          | 0.92 ± 0.42                                   | 0.98 ± 0.52                                       | .343  |
| e-GFR (mL/min/1.73 m²) | 76.0 ± 19.7            | 75.7 ± 21.0                                   | 76.3 ± 18.7                                       | .813  |
| Platelet (10^5/µL)    | 102.8 ± 30.5           | 98.2 ± 34.2                                   | 106.1 ± 27.1                                     | .045  |
| Prothrombin time (s)  | 11.5 ± 0.78            | 11.4 ± 0.67                                   | 11.5 ± 0.83                                       | .299  |
| APF (mg/mL)†          | 13.3 ± 5.25            | 13.4 ± 17.1                                   | 21.8 ± 39.9                                      | .049  |
| HCV genotype 1 (%)    | 184 (73.9)             | 81 (77.9)                                     | 103 (71)                                         | .225  |
| High HCV RNA load (%) | 174 (69.9)             | 73 (70.2)                                     | 101 (69.7)                                       | .927  |
| Interferon experienced (%) | 87 (34.9)              | 38 (36.5)                                     | 49 (33.8)                                        | .654  |
| HBV co-infection (%)  | 15 (6.0)               | 6 (5.8)                                       | 9 (6.2)                                           | .886  |
| FIB-4†                | 5.86 ± 4.03            | 6.03 ± 4.31                                   | 5.74 ± 3.83                                       | .573  |
| APRI†                 | 2.48 ± 2.38            | 2.50 ± 2.39                                   | 2.48 ± 2.39                                       | .943  |
| Advanced fibrosis (%) | 213 (85.9)             | 88 (84.6)                                     | 125 (86.2)                                       | 7.25  |
| HCC (%)               | 49 (19.7)              | 20 (19.2)                                     | 29 (20.0)                                        | .880  |
| Splenomegaly (%)      | 131 (52.6)             | 56 (53.8)                                     | 75 (51.7)                                        | .741  |
| Ascites (%)           | 18 (7.2)               | 7 (6.7)                                       | 11 (7.6)                                         | .797  |

APP = alpha-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; e-GFR = estimated glomerular filtration rate; FIB-4 = fibrosis-4; HCC = hepatocellular carcinoma; DM = diabetes mellitus; APRI = aspartate aminotransferase to platelet ratio index.

† Data are expressed as the mean ± standard deviation.

† Threshold for low vs high baseline HCV RNA load: 400,000 IU/mL.
(including mild, moderate and severe fatty liver [mean platelet count, $110 \times 10^3 / \mu L$]) were actually higher than those without (mean platelet count, $9.9 \times 10^3 / \mu L$) ($P < .01$). This finding may be related to metabolic syndrome and insulin resistance.\textsuperscript{[14–18]} However, only moderate or severe fatty liver was significantly associated with platelet count improvement after DAA treatment. The reason is unclear, and further study is required to clarify this phenomenon. We also found that a lower baseline platelet count significantly predicted platelet count improvement after DAA treatment. This result may only reflect the relatively prominent difference as compared to the higher baseline group.

Splenomegaly is also a key factor for thrombocytopenia in CHC patients. We observed that CHC patients with splenomegaly actually had lower baseline platelet counts than did those without splenomegaly ($93 \times 10^3 / \mu L$ vs $113 \times 10^3 / \mu L$; $P < .001$). However, after DAA treatment, multivariate analyses revealed that platelet count improvement was not significantly associated with the presence of splenomegaly. TPO is involved in the formation of platelets, and TPO levels are related to platelet counts in patients with liver fibrosis or cirrhosis.\textsuperscript{[9,39–41]} Patient TPO levels were not determined in this study, comparisons cannot be made.

### 4.1. Limitations

This study has several limitations. First, did not follow-up the patients long enough to determine long-term outcomes. Whether the observed platelet count improvement persists requires further clarification. However, several short reports have shown that this improvement persisted at least up to 1 year. Second, we did not check the expression levels of cytokines or inflammatory proteins, so we could not fully explain why lower baseline platelet count and more severe fatty liver were associated with the observed rapid platelet count improvement. Further studies are required to explore the pathophysiology underlying this observation.

### Table 2

| Factor                        | Odds ratio | 95% CI       | $P$   |
|-------------------------------|------------|--------------|------|
| Alcoholism                    | 2.448      | 0.891–6.728  | .083 |
| Moderate to severe fatty liver| 2.918      | 1.149–7.400  | .024 |
| AFP                           | 0.987      | 0.974–1.002  | .054 |
| Baseline platelet count       | 0.987      | 0.977–0.996  | .005 |
| AST                           | 0.997      | 0.992–1.002  | .181 |

$^a$ Adjusted for age, gender, alcoholism, moderate to severe fatty liver, baseline alpha-fetoprotein (AFP) level, baseline platelet level, and baseline AST (aspartate aminotransferase) level.
5. Conclusion

Thrombocytopenia is a complication of HCV-related liver disease. DAA treatment can improve this condition during treatment and after short-term follow-up. Lower baseline platelet count and the presence of moderate or severe fatty liver is associated significant improvement in platelet count with DAA treatment.

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Author contributions

Chih-Wei Tseng: statistical analysis, material support, critical revision of the manuscript for important intellectual content.
Kuo-Chih Tseng: material support, critical revision of the manuscript for important intellectual content.
Yen-Chun Chen: material support, drafting of the manuscript.

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