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Non-cirrhotic thrombocytopenic patients with hepatitis C virus: Characteristics and outcome of antiviral therapy

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Abstract

Background and Aim: Thrombocytopenia is frequently observed in patients with chronic hepatitis C virus (HCV) infection and cirrhosis, although it can also be observed in patients without cirrhosis by a virus-mediated phenomenon. This study assessed the prevalence, characteristics, and outcomes of antiviral therapy in patients with chronic HCV infection and thrombocytopenia not associated with cirrhosis.

Methods: The study included 1268 patients with HCV infection and thrombocytopenia enrolled in the phase 3 ENABLE studies that assessed the impact of eltrombopag on achieving a sustained virologic response to pegylated interferon and ribavirin. The study population was subdivided according to baseline FibroSURE test results into patients with non-cirrhosis (FibroSURE < 0.4) and cirrhosis-related (FibroSURE ≥ 0.75) thrombocytopenia.

Results: Compared with patients with cirrhosis-related thrombocytopenia ($n = 995$; 78.5%), non-cirrhotic patients with thrombocytopenia ($n = 59$; 4.6%) were younger (mean age [95% confidence interval (CI)]: 43.9 [40.7–47.2] *vs* 52.7 [52.2–53.3] years; $P < 0.0001$), predominantly female (64% [51–76] *vs* 30% [27–33]; $P < 0.0001$), and less frequently had a Model for End-Stage Liver Disease score ≥ 10 (24% [14–37] *vs* 45% [42–49]; $P = 0.0012$), low albumin levels (≤ 35 g/L; 2% [0–9] *vs* 32% [29–35]; $P < 0.0001$), and prevalence of diabetes mellitus (3% [0–12] *vs* 21% [19–24]; $P = 0.0005$). The sustained virologic response rate was higher in non-cirrhotic patients with thrombocytopenia (46% [95% CI, 33–59] *vs* 16% [14–18]; $P < 0.0001$).

Conclusions: Patients with thrombocytopenia associated with HCV who have lower FibroSURE test results may have better preserved liver function and higher sustained virologic response rates than patients with cirrhosis.

Introduction

Chronic hepatitis C virus (HCV) infection is associated with various extrahepatic manifestations, including thrombocytopenia, which is observed in approximately 25% of patients.[1–3] In these patients, thrombocytopenia has traditionally been ascribed to platelet sequestration within the spleen due to portal hypertension and, more recently, to decreased thrombopoietin production—both conditions associated with advanced fibrosis and cirrhosis.[4–7] No clear correlation has been identified between platelet count and portal pressure; however, thrombocytopenia has been observed in HCV-infected patients without cirrhosis when other mechanisms such as virus-induced immune-mediated platelet destruction have been described as possible (co-)responsible factors for the decreased platelet count.[8–10]

Besides representing a hallmark of advanced disease stage, thrombocytopenia may represent an obstacle to initiation and maintenance of pegylated interferon (PEG-IFN) and ribavirin

(RBV) therapy in patients with chronic HCV infection, and it has been associated with an increased risk of bleeding during antiviral treatment.[11–14] However, in some cases, successful interferon antiviral therapy has been associated with an increase in platelet count during treatment, and there is initial evidence that a proportion of patients with HCV infection and thrombocytopenia may display some peculiar clinical features, although the characteristics and outcome of antiviral therapy according to disease stage in these patients have not been evaluated in adequately sized cohorts.[15–17]

The ENABLE-1 and ENABLE-2 (Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects With Hepatitis C Related Liver Disease; ClinicalTrials.gov identifiers: NCT00516321 and NCT00529568, respectively) studies were phase 3, randomized, placebo-controlled, multicenter trials that enrolled a large cohort of thrombocytopenic (platelet count $< 75 \times 10^9$/L) patients with HCV infection and compensated chronic liver disease who were otherwise good candidates for PEG-IFN and RBV antiviral therapy. These studies demonstrated that eltrombopag, when used as supportive treatment, increases platelet counts to a level sufficient to initiate and maintain PEG-IFN and significantly improves sustained virologic response (SVR) rates to antiviral therapy as compared with placebo.[18] In these studies, severity of disease was also assessed by means of FibroSURE (FS) testing. According to FS test results,[19,20] patients were subdivided into two groups: patients with non-cirrhotic thrombocytopenia and those with cirrhosis-related thrombocytopenia.

This study aimed to assess the demographic, clinical, and virologic characteristics, as well as the outcomes, of PEG-IFN and RBV treatment in patients with non-cirrhotic thrombocytopenia and chronic HCV infection and to compare these features with those of patients with cirrhosis-related thrombocytopenia.

Methods

Patients. The ENABLE-1 and ENABLE-2 studies were conducted in two sequential parts. In part 1, patients received open-label eltrombopag until they reached the platelet count threshold needed to initiate antiviral therapy. In part 2, patients were randomized 2:1 in a double-blind fashion to receive either eltrombopag or placebo in combination with PEG-IFN and RBV. The primary aim of the studies was to evaluate the effect of eltrombopag treatment on SVR. The details of each study's inclusion and exclusion criteria, as well as the characteristics of the patient cohorts, have been described previously.[18] Both ENABLE studies were approved by the institutional review boards and/or ethical committees, as appropriate, at each study center. This study was conducted in accordance with Good Clinical Practice guidelines and all applicable patient privacy requirements, and the principles in the Declaration of Helsinki. All patients enrolled in both studies provided written informed consent prior to study entry.

The ENABLE studies included patients with thrombocytopenia and compensated chronic liver disease, and the FS test was one of the parameters used to grade the severity of liver disease.[18,19] Baseline FS test results were available in 1268 (83.4%) of the 1521 patients enrolled in the ENABLE studies. The FS test uses the results of six biochemical tests (alanine aminotransferase [ALT], gamma-glutamyl transferase, haptoglobin, alpha-2-macroglobulin, total bilirubin, and apolipoprotein A1) with a patient's age and sex to generate a measure of fibrosis and necroinflammatory activity in the liver.[20–23] FS scores correlate to stages of fibrosis, and a comparison of the FS test with liver biopsy showed a negative predictive value of FS < 0.31 of 85% and a positive predictive value of 54% when analyzing a group of 1270 HCV patients.[20] In patients with chronic HCV, the FS test results correlate with the histologic stage of liver fibrosis expressed according to the METAVIR score.[20–23] For the purpose of this study, in line with the FS test results and the METAVIR scoring system, we identified three groups of patients: (i) patients with FS < 0.4, who were classified as patients with non-cirrhotic thrombocytopenia; (ii) patients with FS ≥ 0.75, who were classified as patients with cirrhosis-related thrombocytopenia; and (iii) patients with FS of 0.4 to 0.75, who cannot be adequately classified as patients with or without cirrhosis and were therefore not included in this analysis. Patients with FS test results of 0.4 to 0.75 had demographic characteristics that were similar to those of patients with cirrhosis-related thrombocytopenia, as shown in Table S1. For each patient, we also calculated the Model for End-Stage Liver Disease (MELD) score and the aspartate aminotransferase (AST)/ALT ratio as biochemical indexes related to the severity of liver disease and the patients' prognosis.[24,25]

Efficacy assessments. SVR was defined as the proportion of patients with undetectable serum HCV RNA at 24 weeks after completing antiviral therapy. Rapid virologic response (RVR) and complete early virologic response (EVR) were defined as undetectable serum HCV RNA at week 4 and week 12 of therapy, respectively. EVR was defined as a decrease of 2 $\log_{10}$ or greater in serum HCV RNA at week 12 as compared with baseline. End-of-treatment response (ETR) was defined as undetectable HCV RNA at the end of antiviral therapy (24 weeks for patients with HCV genotypes 2 and 3; 48 weeks for patients with HCV genotype other than 2/3).

Statistical analysis. Continuous data are shown as mean values and 95% confidence intervals (CIs) or as median and interquartile range; categorical data are shown as absolute count, percentage, and 95% CI.

Results

Baseline demographic and clinical characteristics of patients with non-cirrhotic and cirrhosis-related thrombocytopenia. The percentage of patients with non-cirrhotic thrombocytopenia (FS < 0.4) was 4.6% ($n = 59$), while 78.5% of patients ($n = 995$) had cirrhosis-related thrombocytopenia (FS ≥ 0.75), and 16.9% of patients ($n = 214$) had indeterminate FS test results (FS = 0.4–0.75).

The baseline demographic, clinical, and virologic characteristics of the 1054 patients with HCV infection and thrombocytopenia subdivided according to FS test results are shown in Table 1. Patients with non-cirrhotic thrombocytopenia were

Table 1 Baseline demographic, clinical, and virologic characteristics of patients subdivided according to non-cirrhotic and cirrhosis-related thrombocytopenia

Characteristic	Non-cirrhotic (*n* = 59)	Cirrhotic (*n* = 995)	*P*-value
Age, mean, years (95% CI)	43.9 (40.7–47.2)	52.7 (52.2–53.3)	< 0.0001
Female, *n* (%, 95% CI)	38 (64, 51–76)	295 (30, 27–33)	< 0.0001
Body mass index, mean, kg/m^2 (95% CI)	26.8 (25.4–28.2)	27.8 (27.5–28.0)	0.1359
Albumin ≤ 35 g/L, *n* (%, 95% CI)	1 (2, 0–9)	320 (32, 29–35)	< 0.0001
Bilirubin, mean, μmol/L (95% CI)	13.53 (12.23–14.82)	23.63 (23.09–24.18)	< 0.0001
Creatinine, mean, μmol/L (95% CI)	69.7 (66.3–73.1)	70.9 (70.1–71.8)	0.4947
INR, mean (95% CI)	1.18 (1.11–1.24)	1.24 (1.23–1.26)	0.0367
Platelet count, mean, ×10^9/L (95% CI)	56 (52–61)	57 (56–58)	0.7278
HCV genotypes 1, 4, and 6, *n* (%, 95% CI)	42 (71, 58–82)	687 (69, 66–72)	0.9581
HCV RNA, mean, ×10^6 IU/mL (95% CI)	2.03 (1.24–2.82)	1.55 (1.39–1.70)	0.1533
AST/ALT ratio > 0.8, *n* (%, 95% CI)	40 (68, 54–79)	895 (90, 88–92)	< 0.0001
Diabetes mellitus, *n* (%, 95% CI)	2 (3, 0–12)	209 (21, 19–24)	0.0005
Child-Pugh class A, *n* (%, 95% CI)	58 (98, 91–100)	946 (95, 94–96)	0.2513
MELD score ≥ 10, *n* (%, 95% CI)	14 (24, 14–37)	452 (45, 42–49)	0.0012

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.

younger (mean age, 43.9 [95% CI, 40.7–47.2] *vs* 52.7 [52.2–53.3] years), predominantly female (64% [51–76] *vs* 30% [27–33]), less frequently had a serum albumin level below the lower limit of normal (≤ 35 g/L; 2% [0–9] *vs* 32% [29–35]), an AST/ALT ratio > 0.8 (68% [54–79] *vs* 90% [88–92]), prevalence of diabetes mellitus (3% [0–12] *vs* 21% [19–24]), and a MELD score ≥ 10 (24% [14–37] *vs* 45% [42–49]).

Mean baseline platelet counts (95% CI) were 56.1×10^9/L (51.5–60.7) and 56.7×10^9/L (55.9–57.5) in patients with non-cirrhotic and cirrhosis-related thrombocytopenia, respectively. Mean body mass index (26.8 kg/m^2 [95% CI, 25.4–28.2] *vs* 27.8 kg/m^2 [27.5–28.0]), virologic characteristics (genotypes 1, 4, or 6: 71% [58–82] *vs* 69% [66–72]), and viral load (2.03×10^6 IU/mL [1.24–2.82] *vs* 1.55×10^6 IU/mL [1.39–1.70]) were similar in patients with non-cirrhotic and cirrhosis-related thrombocytopenia, respectively.

Virologic response rates in patients with non-cirrhotic and cirrhosis-related thrombocytopenia. Figure 1 shows the virologic response rates at key time points during antiviral therapy in patients with non-cirrhotic and cirrhosis-related thrombocytopenia. In particular, while RVR was similar in the two groups (22% [95% CI, 12–35] *vs* 15% [13–17]; $P = 0.0594$), complete EVR (59% [46–72] *vs* 31% [28–34]; $P < 0.0001$), EVR (76% [63–86] *vs* 55% [52–59]; $P = 0.0007$), ETR (69% [56–81] *vs* 35% [32–38]; $P < 0.0001$), and SVR rates (46% [33–59] *vs* 16% [14–18]; $P < 0.0001$) were higher in patients with non-cirrhotic than cirrhosis-related thrombocytopenia, respectively.

Platelet count dynamics according to antiviral treatment outcome. Figure 2a and b show the dynamics of platelet count (median and interquartile range) during PEG-IFN and RBV treatment according to FS test results in the eltrombopag and placebo arms, respectively. The median platelet count tended to be higher in patients with non-cirrhotic thrombocytopenia throughout the course of antiviral treatment as compared with cirrhosis-related thrombocytopenia in both the eltrombopag (week 4: 128.0×10^9/L *vs* 94.5×10^9/L; week 12: 120.0×10^9/L *vs* 96.0×10^9/L; week 24: 128.5×10^9/L *vs* 95.0×10^9/L; end of treatment: 130.0×10^9/L *vs* 95.5×10^9/L) and placebo (week 4: 80.0×10^9/L *vs* 47.0×10^9/L; week 12: 113.5×10^9/L *vs* 44.0×10^9/L; week 24: 100.1×10^9/L *vs* 43.0×10^9/L; end of treatment: 72.0×10^9/L *vs* 45.0×10^9/L) groups, although this trend was definitely more evident in the latter group of patients. Table 2 shows that, when patients were further subdivided according to SVR, this phenomenon was more marked in patients with non-cirrhotic thrombocytopenia who obtained an SVR, especially in those treated with placebo in whom the increase in platelet counts was more evident due to the absence of the thrombopoietic effect of eltrombopag (Fig. 3a–d).

Safety. Although the incidence of thromboembolic events was similar in the two groups of patients (non-cirrhotic *vs* cirrhotic: 3% [*n* = 2; 95% CI, 0–12] *vs* 3% [*n* = 26; 95% CI, 2–4], respectively), the incidence of hepatic decompensation was lower in patients with non-cirrhotic thrombocytopenia (2% [*n* = 1; 95% CI, 0–9] *vs* 12% [*n* = 116; 95% CI, 10–14], respectively).

Discussion

The present study demonstrates for the first time that a small but significant population of patients with HCV infection and thrombocytopenia has distinct clinical features and treatment responses to interferon that differentiate them from patients with cirrhosis.

Previous studies have shown a prevalence of antiplatelet antibodies as high as 66% in patients with chronic HCV infection, but without a correlation with platelet count, whereas other studies have shown that clearance of HCV during interferon-based antiviral therapy was associated with increased platelet counts in some patients.[15,26,27] This evidence points to the possible existence,

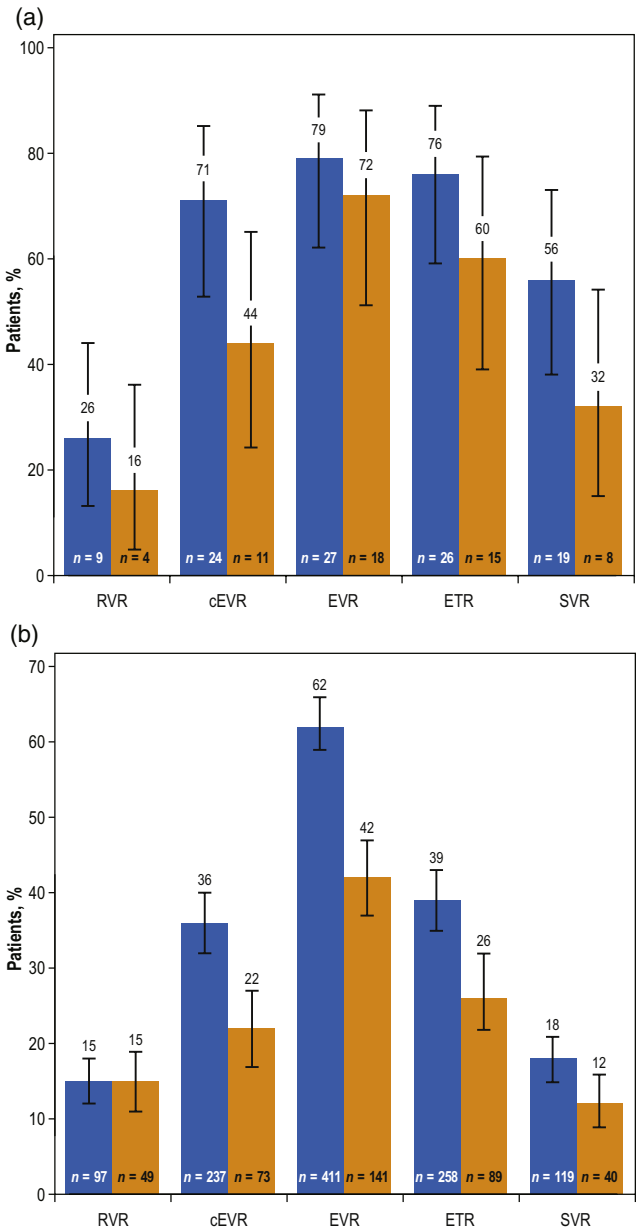

Figure 1 Overall virologic responses in patients by FibroSURE test results at the various treatment milestones in patients with (a) non-cirrhotic and (b) cirrhosis-related thrombocytopenia. Data are shown as percentage (95% confidence interval). cEVR, complete early virologic response; ETR, end-of-treatment response; EVR, early virologic response; RVR, rapid virologic response; SVR, sustained virologic response. ■ Eltrombopag; ■ Placebo.

within the population of patients with HCV infection and thrombocytopenia, of heterogeneous subgroups of patients in which this hematologic abnormality may be due to different mechanisms and whose clinical characteristics and thrombocytopenic response to antiviral therapy have not been thoroughly assessed.

The ENABLE-1 and ENABLE-2 studies were randomized, double-blind, placebo-controlled studies that were performed in order to evaluate the ability of eltrombopag to allow initiation and maintenance of PEG-IFN and RBV therapy in a large series of patients with chronic HCV infection in which thrombocytopenia was the only limiting factor for antiviral treatment initiation.[18] In these studies, the majority of patients had advanced fibrosis or cirrhosis according to FS test results.[18–20,22] However, we observed that approximately 5% of the study population had thrombocytopenia despite FS test results that were compatible with the presence of minimal or absent fibrosis, suggesting that decreased platelet counts were associated neither with the presence of cirrhosis nor presumably with portal hypertension in these patients.[19,20,22]

Despite using different methods for assessing disease stage, a community-based study that evaluated the relationship between severity of liver disease and thrombocytopenia in patients with chronic HCV infection showed that 2.3–5.1% of patients with a platelet count below 100 x10^9/L had ultrasonographic evidence of "normal" or "fatty liver,"[28] a prevalence quite similar to that observed in the present study. In this study, we observed that virologic characteristics (HCV viral load and genotype) were not different in patients with non-cirrhotic and cirrhosis-related thrombocytopenia, although we found that patients with non-cirrhotic thrombocytopenia were more frequently younger and female and had clinical and biochemical features of less advanced liver disease, such as a lower prevalence of a MELD score ≥ 10 and an AST/ALT ratio > 0.8, as compared with patients with cirrhosis-related thrombocytopenia. Previous reports of small series of patients with chronic HCV infection and suspected immune thrombocytopenia have also reported a higher prevalence in women, a finding at odds with the commonly reported greater incidence of HCV infection in men.[15,16,29] In contrast, the prevalence of diabetes mellitus, which is considered to be among the extrahepatic manifestations of HCV infection, was higher in patients with cirrhosis-related thrombocytopenia, a finding consistent with the higher prevalence of this metabolic disease in patients with more advanced liver disease.[30,31] Overall, these findings suggest that chronic HCV infection may also induce thrombocytopenia in a subset of patients with preserved liver function and less advanced disease. This phenomenon is more frequent in women, while no association seems to be evident with viral load and genotype.

We observed that response to antiviral therapy was improved in patients with non-cirrhotic thrombocytopenia as compared with patients with cirrhosis-related thrombocytopenia, with this difference definitely more evident from week 12 of treatment onward. Despite patients' similar baseline virologic characteristics, this finding was likely because of a greater prevalence of unfavorable characteristics (male sex, diabetes, decreased liver synthetic function, and higher MELD scores) in patients with cirrhosis-related thrombocytopenia and to the inherent lower interferon sensitivity of patients with more advanced liver disease.[32,33] SVR rates with PEG/RBV vary depending on HCV genotype and the presence of liver fibrosis/cirrhosis, with patients infected with genotype 2 or 3 and non-cirrhotic patients achieving higher SVR rates.[34–36] The ENABLE population included patients infected with various HCV genotypes, but mostly genotype 1, and most patients had cirrhosis.[18] Lastly, the SVR rates observed in the current study in patients without cirrhosis who had thrombocytopenia were not dissimilar from those seen in non-cirrhotic HCV patients without

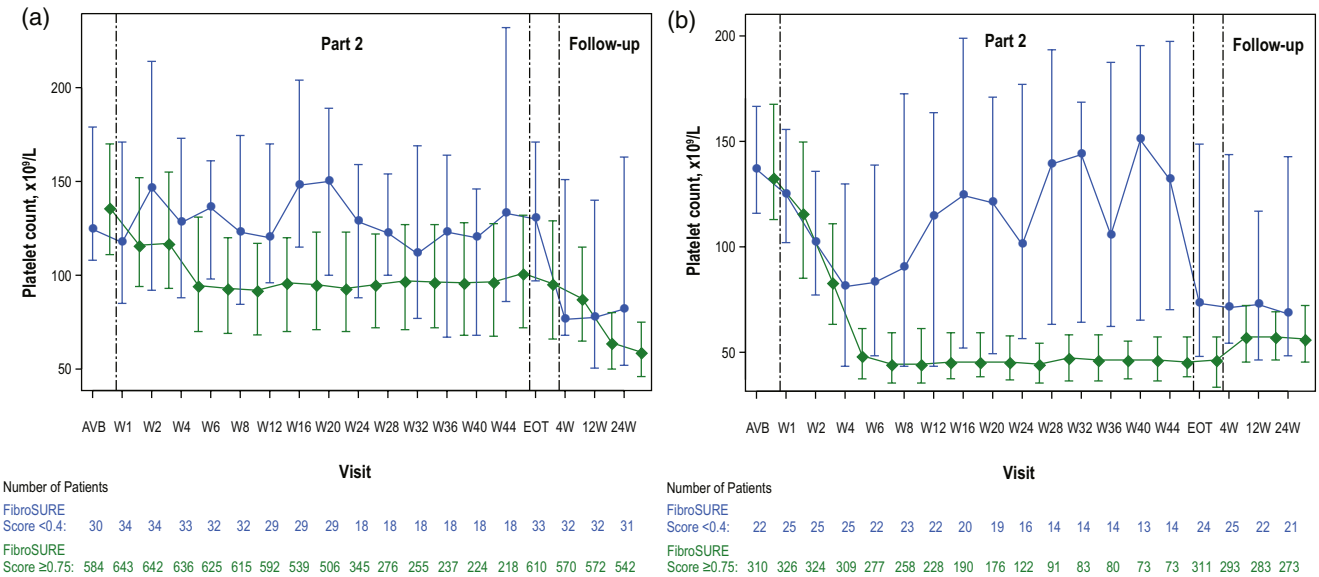

Figure 2 Platelet counts during the antiviral treatment phase according to FibroSURE test results in patients treated with (a) eltrombopag and (b) placebo subdivided according to FibroSURE test results (blue line, non-cirrhotic; green line, cirrhotic). Data are shown as median and interquartile range. AVB, antiviral baseline; EOT, end of treatment; W, week. $P < 0.001$ for FibroSURE < 0.4 *vs* ≥ 0.75 based on post-hoc mixed model for repeated measures (while on treatment) analysis of log platelet values with log baseline platelet, baseline FibroSURE subgroup, and FibroSURE subgroup by visit interaction.

Table 2 Platelet counts during antiviral treatment and at follow-up subdivided according to treatment arm, FibroSURE test results, and response to antiviral treatment

	Placebo				Eltrombopag			
	Non-cirrhotic		Cirrhotic		Non-cirrhotic		Cirrhotic	
SVR	*n*	Platelet count, median (IQR)	*n*	Platelet count, median (IQR)	*n*	Platelet count, median (IQR)	*n*	Platelet count, median (IQR)
Week 4	8	139.5 (99.5–178.5)	40	52.0 (41.5–73.5)	19	150.0 (87.0–178.0)	119	97.0 (74.0–144.0)
Week 12	8	139.1 (124.0–225.5)	40	45.0 (39.5–58.0)	18	125.5 (100.0–159.0)	119	104.0 (79.0–133.0)
Week 24	7	159.0 (97.1–200.0)	17	46.0 (37.0–51.0)	12	151.0 (114.5–212.0)	68	103.0 (74.0–124.5)
End of treatment	8	145.5 (103.7–226.5)	39	44.0 (33.0–59.0)	18	148.5 (105.0–162.0)	119	103.0 (76.0–137.0)
Week 24 follow-up	8	130.0 (88.0–211.0)	40	55.5 (48.0–79.0)	19	94.0 (64.0–172.0)	118	65.0 (50.0–87.0)
Non-SVR	*n*	Platelet count, median (IQR)	*n*	Platelet count, median (IQR)	*n*	Platelet count, median (IQR)	*n*	Platelet count, median (IQR)
Week 4	17	52.0 (35.0–102.0)	269	46.0 (36.0–59.0)	14	117.5 (91.0–152.0)	517	94.0 (70.0–127.0)
Week 12	14	64.2 (39.0–149.0)	188	44.0 (36.0–58.0)	11	114.0 (73.0–217.0)	473	93.0 (69.0–119.0)
Week 24	9	78.0 (44.0–103.0)	105	43.0 (34.0–53.8)	6	85.0 (67.0–105.0)	277	93.0 (72.0–121.0)
End of treatment	16	50.0 (41.0–72.0)	272	45.0 (32.0–56.0)	15	120.0 (60.0–179.0)	491	94.0 (65.0–126.0)
Week 24 follow-up	13	57.0 (27.0–72.0)	233	55.0 (43.0–70.0)	12	58.5 (47.0–129.5)	424	58.0 (46.0–72.0)

IQR, interquartile range; SVR, sustained virologic response.

thrombocytopenia after 24 weeks of PEG/RBV (46.0% *vs* 49.4%).[36] Although similar results were obtained for EVR (76.0% *vs* 60.3–94.9% depending on genotype), RVR tended to be lower in our study (22.0% *vs* 26.5–84.7% depending on genotype).[36] However, it must be emphasized that, in non-cirrhotic patients, the presence of severe thrombocytopenia prevented the beginning of antiviral therapy and that pretreatment with eltrombopag enabled these patients to start PEG-IFN and RBV treatment.[18]

Lastly, the most relevant result of this study is that, looking at the longitudinal modifications of platelet counts during antiviral therapy, it is evident that patients with non-cirrhotic thrombocytopenia tended to have a higher mean platelet count than that of patients with cirrhosis-related thrombocytopenia. This finding was even more evident in the placebo arm of the study, in which patients with non-cirrhotic thrombocytopenia—despite some variability—tended to have median platelet counts above 100×10^9/L

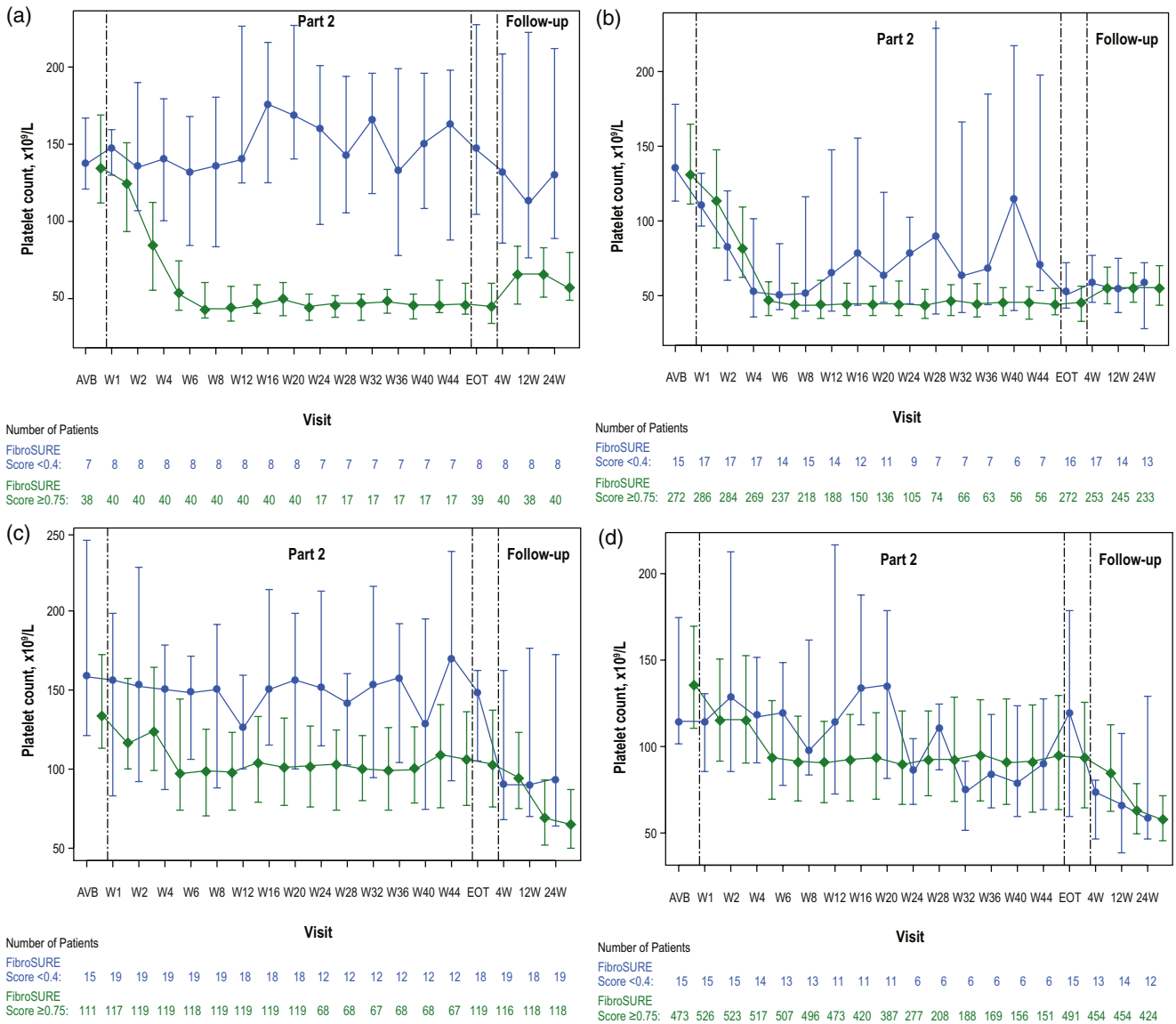

Figure 3 Platelet counts during antiviral therapy in patients subdivided according to treatment received and response to antiviral therapy (placebo [(a) achieving SVR and (b) not achieving SVR]; eltrombopag [(c) achieving SVR and (d) not achieving SVR]) and FibroSURE test results (blue line, non-cirrhotic; green line, cirrhotic). Data are shown as median and interquartile range. AVB, antiviral baseline; EOT, end of treatment; SVR, sustained virologic response; W, week. $P < 0.001$ for FibroSURE < 0.4 *vs* ≥ 0.75 based on post-hoc mixed model for repeated measures (while on treatment) analysis of log platelet values with log baseline platelet, baseline FibroSURE subgroup, and FibroSURE subgroup by visit interaction.

from week 4 onward. Moreover, when placebo-treated patients were subdivided according to antiviral treatment outcomes, we found that the increase in platelet count during treatment was observed mainly in non-cirrhotic patients who cleared HCV infection. These patients had a median platelet count consistently above $130–150 \times 10^9$/L throughout the duration of antiviral therapy and also maintained elevated platelet counts at week 24 of follow-up. These data suggest that, in patients with non-cirrhotic thrombocytopenia, successful antiviral treatment improves platelet counts during and after treatment, raising the possibility that a virus-mediated mechanism may be responsible for decreased platelet count in these patients. The results corroborate previous anecdotal evidence and results obtained in small series of patients.[15,26]

This study has a few limitations, besides being based on a post-hoc analysis. There was no assessment of antiplatelet antibodies, so it cannot be determined if antiplatelet antibodies were more prevalent in patients with non-cirrhotic thrombocytopenia. However, previous studies have shown a high prevalence of antiplatelet antibodies in patients with HCV infection and no correlation with platelet count.[27] Another limitation of the study is inherent in the definition of "non-cirrhotic" or "cirrhosis-related" thrombocytopenia, which was based on the FS test results alone

because a liver biopsy was not required for enrollment into the ENABLE studies.[18] Indeed, FS has shown reliable accuracy for the noninvasive diagnosis of cirrhosis,[19–23] while it showed only modest accuracy for the diagnosis of lower stage liver fibrosis in patients with HCV infection.[37] Thus, it is possible that some patients with low FS test results might have been misclassified as patients with non-cirrhotic thrombocytopenia when they actually had cirrhosis-related thrombocytopenia. This possible limitation of the study is further highlighted by the finding that 24% of patients with non-cirrhotic thrombocytopenia had a MELD score ≥ 10, a score rarely found in patients with mild liver disease.

In conclusion, the results of this study suggest the existence of a small subset of patients with HCV infection and thrombocytopenia, who are predominantly young and female, in which this hematologic abnormality is more frequently associated with features of less advanced liver disease and in which viral clearance may be associated with improvement in platelet counts.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Baseline demographic, clinical, and virologic characteristics of patients subdivided according to FS test results.