




RESEARCH ARTICLE

Change in the hepatic profile of hepatitis C virus genotype 4-infected patients with compensated cirrhosis receiving ombitasvir, paritaprevir, and ritonavir plus ribavirin: A subanalysis of the AGATE-II study

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In AGATE-II, treatment with ombitasvir coformulated with paritaprevir/ritonavir plus ribavirin (RBV) in Egyptians infected with hepatitis C virus genotype 4 resulted in high rates of sustained virologic response at post-treatment week 12. This subanalysis examined the effects of treatment in AGATE-II on liver biomarkers in patients with compensated cirrhosis. AGATE-II was a phase 3, open-label, partly randomized trial of ombitasvir/paritaprevir/ritonavir with weight-based RBV daily once in treatment-naïve or treatment-experienced patients. Patients without cirrhosis received treatment for 12 weeks and patients with compensated cirrhosis were randomized 1:1 to the same regimen for either 12 or 24 weeks. Sixty patients with compensated cirrhosis were randomized to treatment for 12 weeks (n = 31) or 24 weeks (n = 29). In the 12-week arm, significant improvements were observed in biomarkers of liver injury (alanine aminotransferase: -53.7 U/L, $P < 0.001$; aspartate aminotransferase: -35.9 U/L, $P < 0.001$) and liver fibrosis (aspartate aminotransferase to platelet ratio index: -0.987, $P < 0.001$; fibrosis-4 index: -1.165, $P < 0.001$). Similar results were reported in the 24-week arm. Treatment with ombitasvir/paritaprevir/ritonavir plus RBV in hepatitis C virus genotype, 4-infected Egyptians with compensated cirrhosis resulted in improvements in certain biomarkers of liver synthetic function, injury, and fibrosis, independent of treatment duration.

KEYWORDS

chronic hepatitis C, compensated cirrhosis, direct-acting antivirals (DAAs), genotype 4, liver biomarkers

1 | INTRODUCTION

Flaviviridae *Hepacivirus* Hepatitis C virus genotype 4 (HCV GT4) infection accounts for approximately 8% of all HCV infections globally, but it

constitutes 97% of HCV infections in Egypt.¹ Therefore, it can be inferred that HCV GT4 is a leading cause of liver-related morbidity and mortality in Egypt.² A nation-wide program, established in 2006, evaluated more than 1.5 million patients with chronic HCV infection and has treated

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nearly 1.2 million patients using a variety of regimens.³ From 2006 to 2014, patients were treated primarily with pegylated interferon and ribavirin (RBV); thereafter, the treatment was mostly with direct-acting antivirals (DAAs).^{3,4} Long-term follow-up data on the improvement of liver function in patients with advanced fibrosis after treatment with DAAs are limited, but available studies with short-term follow-up have shown that viral elimination leads to improvement in portal hypertension and biomarkers of liver fibrosis.⁵⁻⁷

In European and North American patients with chronic HCV GT4 infection and compensated cirrhosis, 12- or 16-week treatment with the DAA regimen of the NS5A inhibitor ombitasvir (OBV), coformulated with paritaprevir (an NS3/4A protease inhibitor identified by AbbVie and Enanta) and the pharmacokinetic enhancer ritonavir (PTV/r), plus RBV, resulted in sustained virologic response rates at post-treatment week 12 (SVR12) of 97% or 98%, respectively.⁸ This treatment has been associated with improvement in several biomarkers of liver fibrosis and synthetic function.⁷ In the phase 3 AGATE-II study, conducted in HCV GT4-infected patients from Egypt, treatment with OBV/PTV/r+RBV for 12 weeks resulted in SVR12 rates of 94% (94/100; one patient with on-treatment breakthrough, three patients with relapse, one patient with missing SVR12 data, and one patient with premature discontinuation) in patients without cirrhosis.⁹ In those with compensated cirrhosis, SVR12 rates were 97% (30/31; one patient with on-treatment breakthrough) and 93% (27/29; one patient with on-treatment breakthrough and one patient with missing SVR12 data) with 12- and 24-week regimens, respectively.⁹ In this subanalysis of AGATE-II, we examined the effects of OBV/PTV/r+RBV on the biomarkers of liver synthetic function, injury, and fibrosis in HCV GT4-infected Egyptian patients with compensated cirrhosis.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Trial design was described previously.⁹ Briefly, AGATE-II was a phase 3, open-label trial conducted at five sites in Egypt.* Patients without cirrhosis received OBV/PTV/r (25 mg/150 mg/100 mg) with weight-based RBV once daily for 12 weeks. Patients with compensated cirrhosis (Child-Pugh score ≤ 6 at screening) were randomized 1:1 to the same regimen for either 12 or 24 weeks. Patients with compensated cirrhosis were those with a diagnosis of cirrhosis based on a previous or screening liver biopsy (eg, Metavir Fibrosis Score > 3 [including 3/4 or 3-4] or Ishak score > 4), FibroScan score ≥ 14.6 kPa during or within 6 months of screening, or a screening FibroTest score of > 0.72 , and aspartate aminotransferase (AST) to platelet ratio index (APRI) of > 2 . Patients with a FibroScan result that was ≥ 12.5 kPa and < 14.6 kPa; or a FibroTest result that was ≤ 0.72 and an APRI > 2 ; or a FibroTest result that was > 0.72 and an APRI ≤ 2 must have had a liver biopsy

TABLE 1 Patient demographics and baseline disease characteristics for patients with compensated cirrhosis⁹

Characteristic	OBV/PTV/r+ RBV 12 wk n = 31	OBV/PTV/r+ RBV 24 wk n = 29
Male, n (%)	29 (94)	22 (76)
Age, y, mean (SD)	57.3 (6.5)	55.8 (8.0)
BMI, kg/m ² , mean (SD)	29.3 (4.4)	31.0 (4.7)
HCV RNA, log ₁₀ IU/mL, mean (SD)	6.02 (0.62)	5.97 (0.69)
Prior pegIFN/RBV treatment experience, n (%)	16 (52)	14 (48)
Null responder ^a	9 (56)	7 (50)
Partial responder ^a	2 (13)	2 (14)
Relapser ^a	5 (31)	5 (36)
Metavir fibrosis stage, n (%)		
F3	1 (3) ^b	0
F4	30 (97)	29 (100)
Platelet count, $\times 10^9$ /L, median (range)	141 (46-365)	125 (59-238)
Albumin, g/L, median (range)	41 (34-53)	40 (31-54)
AST, U/L, median (range)	55 (24-177)	57 (17-167)
ALT, U/L, median (range)	67 (26-188)	68 (16-189)
White blood cell count, $\times 10^9$ /L, median (range)	5.2 (2.1-10.5)	5.9 (2.8-10.5)

ALT, alanine aminotransferase; AST aspartate aminotransferase; BMI, body mass index; HCV, hepatitis C virus; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; pegIFN, pegylated interferon; RBV, ribavirin; SD, standard deviation.

^aPercentage calculated from the subpopulation of treatment-experienced patients.

^bOne patient without cirrhosis was miscategorized as having compensated cirrhosis at the time of enrollment and was assigned to the 12-week arm.

performed before screening showing evidence of cirrhosis; or, in the absence of an available biopsy result before screening, may have undergone a liver biopsy during screening to confirm cirrhosis. A patient with an exclusionary FibroTest but inclusionary FibroScan (or vice versa) was not eligible without a qualifying biopsy. Patients were followed up for 48 weeks after treatment. Eligible patients were adults chronically infected with HCV GT4 for at least 6 months (plasma HCV RNA > 1000 IU/mL at screening), treatment-naïve or previously treated with pegylated interferon/RBV (null responders, partial responders, or relapsers). Patients coinfecting with hepatitis B, HIV, or any other HCV genotype were excluded. Patients with a history of hepatic decompensation were also excluded.

This study was performed in accordance with the International Conference of Harmonisation guidelines, applicable regulations, and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Ethics approval was granted by each study site (see the Supporting

*ClinicalTrials.gov, NCT02247401.¹

Information Materials and Methods). All patients gave a written informed consent.

2.2 | Analyses

In this post hoc analysis, mean changes from baseline to post-treatment week 48 (PTW48) in biomarkers of liver synthetic function, liver injury, and liver fibrosis were assessed for patients with compensated cirrhosis. Markers of hepatic synthetic function were international normalized ratio (INR), albumin, and total bilirubin; markers of liver injury were alanine aminotransferase (ALT) and AST; markers of liver fibrosis were platelet count, APRI, and fibrosis-4 (FIB-4) index.

2.3 | Statistical analysis

All patients who received at least one dose of study drug were included in the analyses. Baseline was defined as the last value collected before the first dose of study drug. Change from baseline was evaluated with the Wilcoxon signed-rank test.

3 | RESULTS

3.1 | Patients

Out of 182 patients screened between November 4, 2014 and March 16, 2015, 160 patients were enrolled in the trial: 100 without cirrhosis and 60 with compensated cirrhosis (12-week arm, $n = 31$; 24-week arm, $n = 29$). Patient demographics and baseline disease characteristics for patients with compensated cirrhosis, who

are included in this subanalysis, were reported previously.⁹ There were no clinically relevant differences in patient demographics or baseline disease characteristics between the two treatment arms (Table 1). In the 12-week arm, there was one (3%) patient without cirrhosis (Metavir fibrosis stage F3) who was miscategorized as having compensated cirrhosis.

3.2 | Liver synthetic function

At PTW48, there were statistically significant improvements compared with baseline in mean total bilirubin for the 24-week arm, although the baseline and PTW48 values for both treatment arms were within normal limits (Figure 1A). Mean albumin was within normal limits at baseline and PTW48 for both treatment arms (Figure 1B). Mean INR increased slightly from baseline for both the 12- and 24-week treatment arms but remained near the 1.1 normal range (Figure 1C).

3.3 | Liver injury

At PTW48, there was an over threefold reduction in ALT (Figure 2A) and an approximately 2.5-fold reduction in AST (Figure 2B) in both the 12- and 24-week treatment arms. For both arms, the mean ALT and AST values were elevated at baseline and improved to values within normal limits at PTW48.

3.4 | Liver fibrosis

Treatment with OBV/PTV/r+RBV resulted in statistically significant improvements at PTW48 in APRI (Figure 3A) and FIB-4 scores

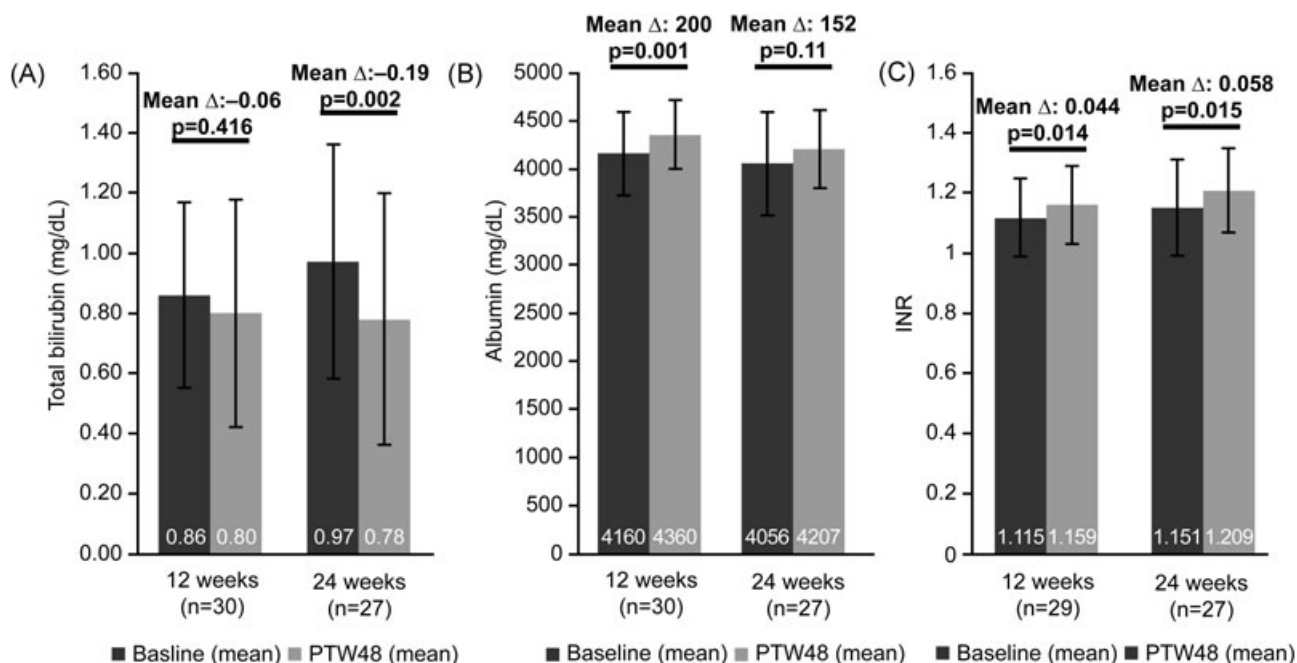


FIGURE 1 Mean changes from baseline to post-treatment week 48 in biomarkers of liver synthetic function in patients with compensated cirrhosis. The error bars represent the standard deviation of the mean. INR, international normalized ratio; PTW, post-treatment week

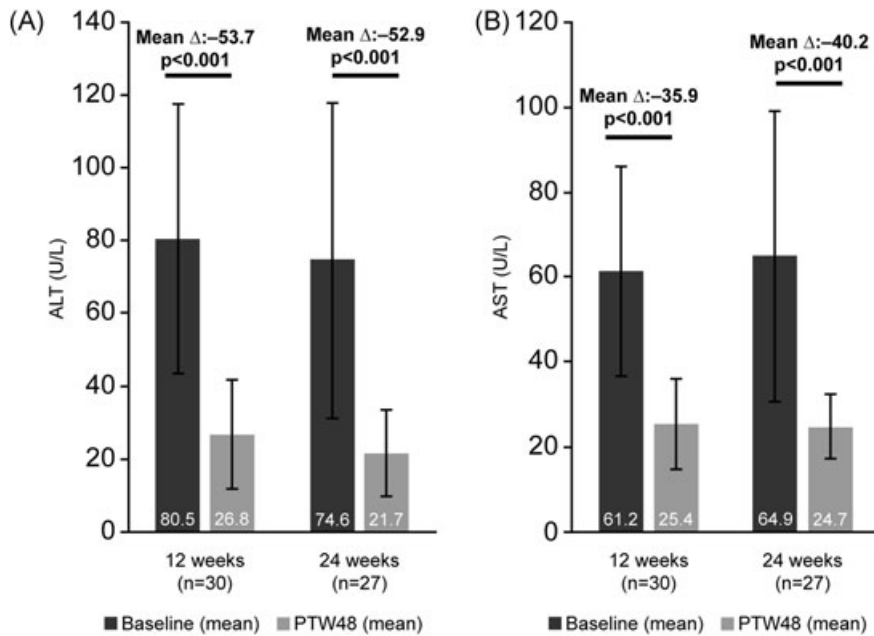


FIGURE 2 Mean changes from baseline to post-treatment week 48 in biomarkers of liver injury in patients with compensated cirrhosis. The error bars represent the standard deviation of the mean. ALT, alanine aminotransferase; AST, aspartate aminotransferase; PTW, post-treatment week

(Figure 3B) in both treatment arms. There was no clinically meaningful effect on platelet count (Figure 3C).

4 | DISCUSSION

Our results suggest that in chronic HCV GT4-infected Egyptian patients with compensated cirrhosis, antiviral treatment with OBV/PTV/r+RBV for 12 or 24 weeks resulted in improvements in various hepatic biomarkers at PTW48.

There are limited data on the effect of DAA therapies on liver biomarkers in HCV GT4-infected Egyptians with compensated cirrhosis. A retrospective study of 337 Egyptian patients with or without cirrhosis, predominantly infected with HCV GT4, found significant improvements in platelet count, ALT levels, and AST levels in cirrhotic patients after a sofosbuvir-based DAA treatment, with 81% of patients with cirrhosis experiencing improvement in liver stiffness at post-treatment week 12 (PTW12).⁶ Conversely, a similar retrospective study of 272 HCV GT4-infected Egyptian patients with or without cirrhosis treated sofosbuvir-based DAA regimens found

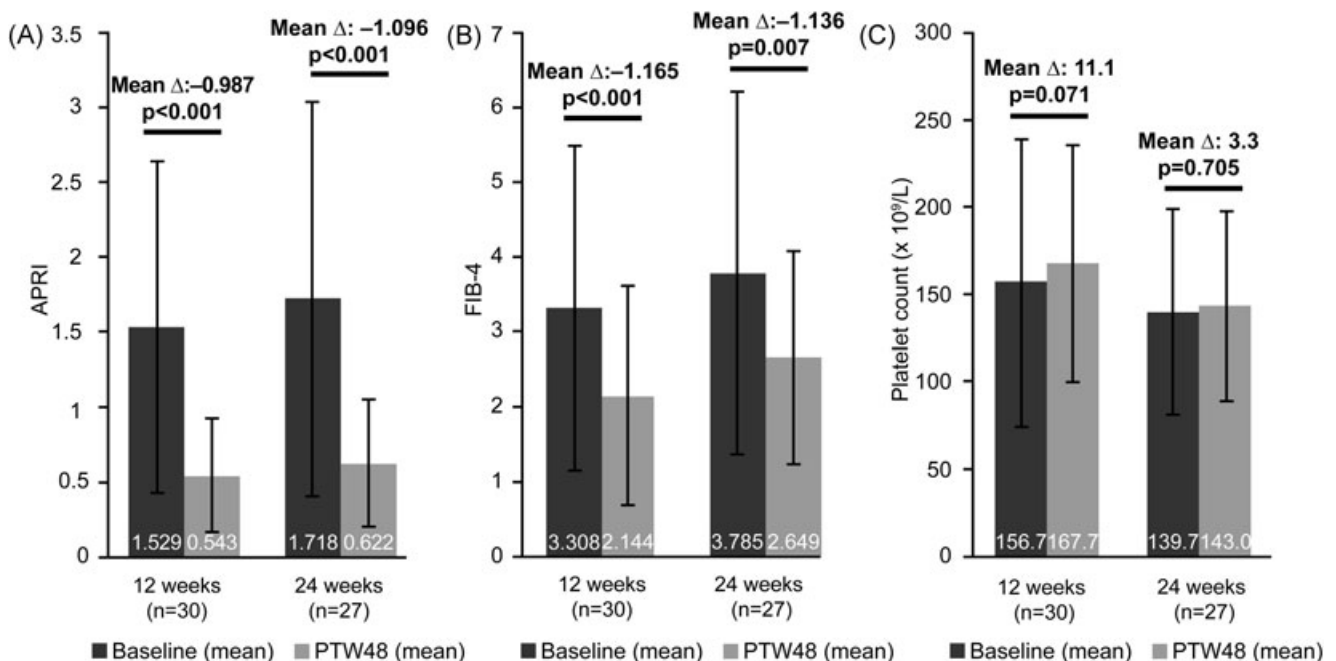


FIGURE 3 Mean changes from baseline to post-treatment week 48 in biomarkers of liver fibrosis in patients with compensated cirrhosis. The error bars represent the standard deviation of the mean. APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4; PTW, post-treatment week

significant increases in mean bilirubin and INR from baseline to the end of treatment among cirrhotic patients, suggesting worsening of liver function.¹⁰ In a smaller single-center study evaluating 50 HCV GT4-infected Egyptian patients with or without cirrhosis treated with simeprevir plus sofosbuvir for 12 weeks, significant improvements were observed in albumin, bilirubin, INR, AST, and platelet count at PTW12 among all patients.¹¹

Our results are generally consistent with post hoc observations from the AGATE-I study, in which treatment with OBV/PTV/r+RBV for 12 or 16 weeks in HCV GT4-infected patients with compensated cirrhosis from Europe and North America resulted in improvements in albumin, alpha-fetoprotein, ALT, AST, APRI, and FIB-4 by PTW12.⁷ Trials of OBV/PTV/r+dasabuvir+RBV in patients with compensated cirrhosis include TURQUOISE-II, which evaluated 12- or 24-week treatment in GT1-infected patients from Europe/North America,¹² and ONYX-II, which evaluated 12-week treatment in GT1b-infected patients from Asia.¹³ Post hoc assessments of these trials suggested improvements in several biomarkers of liver function up to PTW48.^{12,13} In a pooled analysis of the TURQUOISE-II and TOPAZ-II studies, patients with compensated cirrhosis treated with OBV/PTV/r+dasabuvir+RBV showed significant fibrosis regression, as measured by FibroTest, from baseline to PTW12.¹⁴ This effect was reported both in patients who achieved SVR12 and in those who did not, although patients who did achieve SVR12 had a statistically greater reduction in fibrosis.¹⁴

A limitation of this analysis was the small sample size of the study, so these results must be confirmed with larger studies. In addition, trials using histologic assessments of fibrosis are needed to confirm these results and to account for any effect that necroinflammation may have on fibrosis indices and elasticity quantification.

In conclusion, improvements in certain biomarkers of liver function (total bilirubin and albumin), liver injury (ALT and AST), and liver fibrosis (APRI and FIB-4 scores) were observed after antiviral treatment with DAAs. Effective DAA regimens are expected to improve the hepatic profile of HCV-infected cirrhotic patients due to viral eradication, highlighting the importance of initiating therapy in HCV GT4-infected Egyptians with cirrhosis.

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CONFLICTS OF INTEREST

I Waked is speaker, advisory board member, and/or investigator in AbbVie, BMS, Gilead, Janssen, Merck, Onxio, Pharco Pharmaceuticals,

and Roche; G Esmat participated in AbbVie-sponsored clinical studies; R Fouad is investigator in AbbVie, Gilead, and Pharco Pharmaceuticals; N Allam is investigator in AbbVie, BMS, and Pharco Pharmaceuticals; M Hassany is investigator in AbbVie, Janssen, and Gilead and speaker in AbbVie; M Mohey participated in AbbVie-sponsored clinical studies; G Shiha participated in AbbVie-sponsored clinical studies; R Soliman is investigator in AbbVie; RB Qaqish is the employee of Pharmacyclics LLC, an Abbvie company; was a former employee of AbbVie; and may own AbbVie stock or options; C Hall is the employee of AbbVie and may hold stock or options; NN Alami is the employee of AbbVie and may hold stock or options; S Kopecky-Bromberg is the employee of AbbVie and may hold stock or options; and N Mobashery is the employee of AbbVie and may hold stock or options.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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