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Effect of fibrosis on adverse events in patients with hepatitis C treated with telaprevir

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SUMMARY

Background—Data about adverse events are needed to optimise telaprevir-based therapy in a broad spectrum of patients.

Aim—To investigate adverse events of telaprevir-based therapy in patients with and without advanced fibrosis or cirrhosis in a real-world setting.

Methods—Data on 174 hepatitis C-infected patients initiating telaprevir-based therapy at Mount Sinai and Montefiore medical centres were collected. Biopsy data and FIB-4 scores identified patients with advanced fibrosis. Multivariable fully adjusted models were built to assess the effect of advanced fibrosis on specific adverse events and discontinuation of treatment due to an adverse event.

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Author contributions: Kian Bichoupan performed the acquisition, analysis and interpretation of data; drafting of manuscript. Emily R. Giannattasio and Kwaku Marfo performed the acquisition of data. Valérie Martel-Laferrrière, Joseph A. Odin, Lawrence U. Liu, Thomas D. Schiano, Ponni Perumalswami, Meena Bansal, Paul J. Gaglio, Harmit Kalia and Douglas T. Dieterich performed the acquisition, analysis and interpretation of data; critical revision of manuscript. Jonathan M Schwartz, Andrea D. Branch and John F. Reinus performed the study concept and design; drafting of manuscript. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Results—Patients with ($n = 71$) and without ($n = 103$) advanced fibrosis were similar in BMI, ribavirin exposure, gender, prior treatment history, haemoglobin and creatinine, but differed in race. Overall, 47% of patients completed treatment and 40% of patients achieved SVR. Treated patients with and without advanced fibrosis or cirrhosis had similar rates of adverse events; advanced fibrosis, however, was independently associated with ano-rectal discomfort ($P = 0.03$). Three patients decompensated and had advanced fibrosis. The discontinuation of all treatment medications due to an adverse event was significantly associated with older age ($P = 0.01$), female gender ($P = 0.01$) and lower platelets ($P = 0.03$).

Conclusions—Adverse events were common, but were not significantly related to the presence of advanced fibrosis or cirrhosis. More critical monitoring in older and female patients with low platelets throughout treatment may reduce adverse event-related discontinuations.

BACKGROUND

Approximately 3% of individuals worldwide have chronic hepatitis C virus (HCV) infection.¹ HCV infection is a major cause of liver cancer and cirrhosis and a leading indication for liver transplantation.² Prior to 2011, treatment with pegylated interferon and ribavirin was the standard of care for therapy of hepatitis C, but only approximately 45% of treated patients were cured.³ Therapy of genotype-1 hepatitis C with combination pegylated interferon, ribavirin and a protease inhibitor (triple therapy) is now recommended as the standard of care for most individuals who are treatment candidates.⁴

Registration trials suggest that adverse events are more common in patients treated with triple therapy than in those treated with pegylated interferon and ribavirin (dual therapy) alone.^{5, 6} For example, patients treated with triple therapy including telaprevir (TVR) or boceprevir were more likely to develop one or more adverse events including rash, anaemia, pruritus, anorectal symptoms, nausea and diarrhoea.^{5–8}

Since the United States Food and Drug Administration approved TVR in 2011 for use as therapy of genotype-1 HCV infection, we have observed unexpectedly frequent and severe adverse events in our patients treated with this regimen. We collected data regarding the side-effect profile of TVR in clinical practice. It was our hypothesis that, in everyday clinical practice, discontinuation rates of TVR were higher and adverse events more numerous and severe than those reported in registration trials. Contrasting registration-trial and real-world results have been described in patients with HCV infection treated with pegylated interferon and ribavirin alone, with SVR rates differing by as much as 31–61%.⁹ As TVR registration trials had few patients with advanced fibrosis or cirrhosis, we investigated the effect of advanced fibrosis on the incidence of adverse events in treated individuals, and evaluated risk factors for treatment discontinuation due to an adverse event.

PATIENTS AND METHODS

Patients and treatment

A consecutive series of patients with genotype-1 HCV infection treated at Mount Sinai Medical Center, New York, NY or Montefiore Medical Center, Bronx, NY were included in this study. Informed consent was waived for this IRB-approved study, as this study was

observational and no changes to clinical care or clinical tests were made. Data were collected through chart review. The Einstein Human Research Protection Program (HRPP)/ Montefiore Medical Center IRB & the Mount Sinai Program for Protection of Human Subjects/Mount Sinai IRB approved this study. Patients began treatment between May 2011 and February 2012. All patients that received at least one dose of HCV medication were included. Post-liver-transplant patients and individuals co-infected with HIV or hepatitis B virus were excluded from the analysis. All patients had detectable HCV RNA (COBAS TaqMan assay, Roche Molecular Systems, version 2.0; Branchburg, NJ, USA) prior to therapy. Treatment was supervised by a clinical staff at each participating institution experienced in treating HCV and managing side effects of therapy. Patients were treated with telaprevir (Vertex Pharmaceuticals, Cambridge, MA, USA), peginterferon alfa-2a or peginterferon alfa-2b and weight-based ribavirin in accordance with standard treatment guidelines.^{4, 10} Viral load above 1000 IU/mL between weeks 4 and 24, detectable after week 24, or viral breakthrough was considered virological failure. Patients received the standard 48 weeks of treatment beginning with 12 weeks of triple therapy followed by an additional 36 weeks of dual therapy. Previously untreated patients and prior relapsers without cirrhosis were eligible for response-guided therapy, defined as 12 weeks of TVR followed by 12 weeks of dual therapy with pegylated interferon and ribavirin alone. Viral loads at baseline, weeks 4 and 12, and 12 weeks after the end of treatment are presented. A sustained virological response was defined as the absence of HCV viral RNA 12 weeks after the end of treatment (SVR-12).

Adverse events and treatment discontinuation

Data about adverse events were obtained from medical records. Definitions of severe adverse events are provided in Table S1. Erythropoietin (EPO) use was permitted. EPO use, discontinuation of telaprevir alone or of all three drugs, treatment week at discontinuation and the reason for discontinuation (virological failure or adverse event) during therapy were recorded.

Clinical and demographic patient characteristics

Clinical and demographic patient characteristics were recorded. Racial and ethnic data are based on self-reporting. Patients were grouped into those with F0-F2 or F3-F4 (METAVIR) fibrosis according to biopsy results if available, or by FIB-4 score ($\text{age [years]} \times \text{AST [U/L]} / \text{Platelet count [10}^9\text{/L]} \times \text{ALT [U/L]}^{1/2}$)¹¹ with values ≥ 3.25 designating F3-F4 fibrosis.¹² For a sub-group analysis comparing cirrhotics with noncirrhotics, patients without biopsies but elevated FIB-4 scores were investigated for clinical signs of cirrhosis.

Statistical analysis

Data were recorded in an Excel spreadsheet and then exported to SPSS 20.0TM (SPSS Inc, Chicago, IL, USA). Analyses were performed on data from patients who received at least one dose of telaprevir, pegylated interferon and ribavirin, according to an intention-to-treat principle (ITT). Quantitative baseline descriptive variables were expressed as median with inter-quartile range; qualitative variables were expressed as the absolute number and

proportions. Chi-square tests were used to compare categorical variables, two-tailed *t*-tests and student's *t*-tests or Mann–Whitney *U*-tests were used to compare continuous data.

The frequency of adverse events and treatment discontinuation in all treated patients were determined. Univariable and fully adjusted multivariable logistic regression models were built to determine factors associated with each individual adverse event and discontinuation to treatment due to an adverse event. The factors in the base model included age, gender, an interaction term between age and gender, race, prior treatment history (naïve/relapser vs. nonresponder/intolerant), per cent normal haemoglobin (baseline haemoglobin/lower limit of normal haemoglobin $\times 100$), baseline log of HCV viral load and finally metavir F3–F4 fibrosis. For the discontinuation due to adverse event model, baseline platelets were added. Data were analysed using SPSS 20.0™ (SPSS Inc.). A *P* value of less than 0.05 was considered significant.

RESULTS

Demographic and clinical characteristics of treated patients

Analyses were performed on treatment outcomes in 174 patients. Clinical and demographic data are presented in Table 1. The median age of patients was 58 years (IQR: 52–62). Sixty-two per cent were male. One hundred and seven patients (67%) were white, 41 (23%) were black, 7 (4%) identified themselves as other and the race of 10 (6%) was unknown. Fifty nine of 174 patients (34%) reported their ethnicity as Hispanic; 55/59 (93%) as black non-Hispanic. The median log HCV viral load at baseline was 6.41 (6.02–6.85). Overall, 56/174 (32%) were previously untreated. The median BMI of treated individuals was 27.0 kg/m² (IQR: 24.7–30.2); 31 (18%) had diabetes mellitus. Median starting dose of ribavirin was 1200 mg/day (IQR: 1000–1200 mg/day). Median ribavirin exposure in the entire group was 13.7 mg/kg (IQR: 12.6–15.3). Liver biopsy results for 104 patients (60%) were available. IL28B data were only available for 27 patients (16%); five were genotype CC. Combining these data with the calculated FIB-4 score, we estimated that 71 members of the cohort (41%) had advanced fibrosis or cirrhosis (F3–F4). A comparison of patients with and without advanced fibrosis/cirrhosis can be seen in Table 1. Both fibrosis groups were similar in BMI, ribavirin exposure, gender, prior treatment history, haemoglobin, and creatinine, but differed in race with more blacks in the lower fibrosis group.

Treatment outcomes

Of the 174 patients that were treated, 83 (47%) completed treatment. Of the patients who completed treatment, 25 (14%) completed RGT and 58 (33%) completed 48 weeks. The median duration of treatment was 24 weeks (IQR: 12–48). Overall, 69 (40%) patients achieved SVR. The rates of SVR for naïve, nonresponders, relapsers and those intolerant to treatment were 50%, 29%, 52% and 14%, respectively. Treatment was discontinued in 52 (30%) patients due to virological failure and 39 (22%) due to adverse events at any time during therapy. At weeks 4 and 12, 37% and 42% of patients had no detectable HCV RNA, respectively. Within the telaprevir-phase, TVR was discontinued in 36 (21%) patients due to adverse events. Nine patients (5%) who stopped TVR due to adverse events continued

therapy with pegylated interferon and ribavirin. Forty-nine patients (28%) stopped all three medications within the TVR phase.

Adverse events and risk factors

Adverse event frequencies in the low-fibrosis and advanced fibrosis or cirrhosis groups are presented in Table S1. Separate tables showing the frequency of adverse events in Hispanic patients and cirrhotic patients can also be seen in Tables S11 and S12. Reasons for hospitalisation varied greatly and included: extremity inflammation ($n = 2$), syncope/shortness of breath ($n = 2$), infection ($n = 3$), kidney insufficiency ($n = 3$), hypokalemia ($n = 2$), hyperkalemia ($n = 1$), numbness ($n = 1$), dermatitis ($n = 1$), decompensated cirrhosis ($n = 2$), colitis ($n = 1$), arrhythmia ($n = 1$) and acute appendicitis ($n = 1$). The most common reason for hospitalisation was severe anaemia (8/29). In univariable analysis, frequency and severity of adverse events were similar in patients with and without advanced fibrosis or cirrhosis, with the exception of hospital admissions ($P = 0.03$) and decompensation of liver disease ($P = 0.04$). Fully adjusted multivariable models for these events, however, showed that the only adverse event associated with advanced fibrosis or cirrhosis was ano-rectal discomfort (OR: 2.3; 95% CI: 1.07–4.98).

Severe anaemia (Table S2) was associated with age (OR: 1.11; 95% CI: 1.02–1.28), per cent normal haemoglobin (OR: 0.95; 95% CI: 0.91–0.99) and BMI (OR: 0.88; 95% CI: 0.79–0.99). Severe fatigue (Table S3) was associated with per cent normal haemoglobin (OR: 1.04; 95% CI: 1.01–1.08). In addition to fibrosis, ano-rectal discomfort (Table S4) also was associated with per cent normal haemoglobin (OR: 1.05; 95% CI: 1.01–1.09). Hypokalemia (Table S5) was associated with per cent normal haemoglobin (OR: 1.05; 95% CI: 1.01–1.10). Treatment history with nonresponse and intolerance to treatment was significantly associated with skin burning (Table S6) (OR: 1.06; 95% CI: 1.01–1.11). Black race (OR: 5.23; 95% CI: 1.97–13.86) and treatment history with nonresponse or intolerance to treatment (OR: 0.23; 95% CI: 0.09–0.61) were associated with hospital admissions (Table S7). No baseline factors were associated with AKI (Table S8), severe rash (Table S9) or depression (Table S10). Importantly, of the three patients with hepatic decompensation, three developed ascites and one patient also developed hepatic encephalopathy while on therapy. All patients who had a symptom of decompensated liver disease also had advanced fibrosis or cirrhosis.

EPO use also was reviewed. We found significantly higher rates of treatment completion in the group that received EPO as compared with the group that did not (45/71 (63%) vs. 38/103 (37%), $P < 0.01$). The rates of SVR in the group that received EPO and did not receive EPO were 48% and 37%, respectively, but this result was not significant ($P = 0.06$).

Through univariable analyses of adverse event profiles in Hispanic and non-Hispanic patients in subgroup analysis (Table S11), we observed significantly less fatigue in Hispanic than non-Hispanic patients (14% vs. 40%). In a comparison of known cirrhotics with non-cirrhotics, a greater percentage of cirrhotic patients experienced at least one hospitalisation (Table S12).

Modelling treatment discontinuation due to adverse events

The fully adjusted logistic regression model for discontinuation due to an adverse event is presented in Table 2. Age (OR: 1.12; 95% CI: 1.03–1.23), female gender (OR: 7791.69; 95% CI: 9.09–6 675 822.19), the interaction between age and gender (OR: 0.87; 95% CI: 0.77–0.97), and platelets (OR: 0.99; 95% CI: 0.98–0.99) were independently associated with discontinuation of treatment due to an adverse event. In a separate fully adjusted logistic regression model, cirrhosis (Metavir F4) and Hispanic ethnicity were not associated with discontinuation due to adverse events.

DISCUSSION

We analysed the occurrence rates of adverse events and treatment discontinuation during TVR in patients with genotype-1 HCV infection, with special attention to individuals with advanced fibrosis or cirrhosis. In addition, we identified factors associated with treatment discontinuation due to adverse events and other factors that were associated with specific adverse events.

Most importantly, we found the presence of advanced fibrosis or cirrhosis to have no effect on the safety of TVR. Through a multivariable fully adjusted model, fibrosis stage had no effect on drug discontinuation due to adverse events. Older age, lower haemoglobin and lower BMI were all significantly associated with severe anaemia. Higher levels of haemoglobin also were associated with fatigue, hypokalemia and ano-rectal discomfort. This could be explained by the fact that patients with higher haemoglobin levels were likely to remain on treatment longer and were thus exposed to more drug. We were surprised by the association between previous treatment history and skin burning, but are aware that our sample size is small. Our most important finding regarding adverse events was the strong associations between black race and naïve or prior-relapse patients with hospital admissions.

Our results reflect the fact that experience in daily clinical practice (effectiveness) may be different from that in registration trials (efficacy).¹³ The high rate of treatment discontinuation due to adverse events in members of our cohort was not surprising as randomised controlled trials recruit lower risk patients that are intensely monitored. In the ADVANCE⁵ and REALIZE⁶ trials, 73% and 62% of telaprevir-treated patients completed therapy, respectively. Our treatment completion rate of 47% highlights the effect that clinical-trial monitoring and patient selection may have on efficacy. In addition, adverse events caused 22% of our patients, but only 10–13% of trial participants, to discontinue therapy. In our study, prior treatment was not associated with discontinuation due to an adverse event. Other studies, notably CUPIC (cite here), have provided additional data regarding results of TVR in well-compensated cirrhotics.

Differences in the patient populations studied may help explain why our real-world treatment results differ from those of the registration trials. Our study included older patients, more patients with advanced fibrosis or cirrhosis, more black and Hispanic patients, and larger patients (BMI and weight) than did the registration trials. In addition, our inclusion and exclusion criteria were more flexible than those found in randomised

controlled trials. As a result, our patients may have been less adherent and sicker than those in clinical trials.

The issue of the ageing HCV population is one that clinicians must increasingly address. In our patients, older age was significantly associated with treatment discontinuation of all drugs due to an adverse event. The mean patient ages in REALIZE⁶ and ADVANCE⁵ were 51 (Range: 23–69) and 49 years (Range: 19–69) respectively. The mean age of our patients was 56 years and the median age 58 years with a range of 26–74. We treated 17 patients (10%) over age 65 years; data on patients over age 65 years were lacking in the registration trials.¹⁰ Recently, Hu *et al.*¹⁴ reported poorer SVR rates and greater treatment withdrawal rates during 24 weeks of dual therapy in geriatric as compared with younger patients. Older patients in their study also were more likely to relapse. The effect of age on safety and SVR was investigated in two other studies, but no significant association was found, possibly because of small sample sizes.^{15, 16} Our finding suggests that the influence of age on the effectiveness of future treatments be investigated.

Anaemia is the most difficult adverse event to control during triple therapy with a protease inhibitor-containing regimen. In our patients, severe anaemia was associated with older age, lower baseline haemoglobin and lower BMI. These same predictive factors also have been found by Butt *et al.* in HCV-HIV co-infected patients being treated with long-term pegylated interferon alfa-2a and ribavirin.¹⁷ As pegylated interferon causes suppression of hematopoiesis and ribavirin causes haemolysis,^{18–20} lower BMI may lead to greater ribavirin exposure resulting in more anaemia. Interestingly, we saw a strong relationship between EPO use and the completion of therapy, suggesting that improved prediction and management of anaemia may enhance treatment completion rates. Note must be made of the fact that ribavirin dose reductions could not be obtained for all patients in our study limiting the assessment of the effect of growth factors on response.

Telaprevir treatment is only indicated in patients with compensated (Child-Pugh class A) cirrhosis.⁴ The overall number of patients with bridging fibrosis or cirrhosis in ADVANCE was only 21% of the entire cohort.⁵ Our study provides more information about the effect of fibrosis stage on treatment-related side effects. With the exception of ano-rectal discomfort, we found no significant difference in the side-effect profile of TVR in patients with or without advanced liver fibrosis. We suspect that the difference in rates of ano-rectal discomfort was due to immune compromise in patients with advanced fibrosis.^{21, 22} Our study provides more information about the effect of fibrosis stage on treatment-related side effects.

Our study also provides additional information on the relationship between race and treatment safety. Only 7% of patients in ADVANCE were black and only 10% were Hispanic. In the REALIZE study, 4% of patients were black and 9% were Hispanic in the nonlead-in telaprevir group. Twenty-two per cent of patients in our cohort were black and 32% were Hispanic. We did not find race to be predictive of treatment discontinuation due to an adverse event. This can be explained partially by the small effect of race and ethnicity on pharmacokinetic properties of ribavirin and pegylated interferon reported by Brennan *et*

*al.*²³ Other work has shown that black patients treated with dual therapy have lower SVR rates than other individuals.^{24–26}

Our study was limited by relatively small sample size, the use of medical records as a source of information and lack of biopsy data for all patients, which may have caused some patients in our cohort to be misclassified as having either F0–F2 or F3–F4 fibrosis. Collected data were based on standard clinical treatment. For this reason, ITPA genotype and IL28b data were lacking, preventing us from building meaningful SVR models. In addition, during the implementation of any new treatment regimen, there may be a learning curve with respect to patient selection and side-effect management. Our study was conducted in an academic medical setting where patients may be different from those in other private practice settings as well as in clinical trials. The house staff and physician extenders assessed adverse events at every visit and in phone conversations. Finally, it must be understood that we only observed associations between observed factors in our study group and outcomes. We do not construe these factors to be the sole cause of these adverse events and discontinuations.

Recently, Hezode *et al.* published a study examining the safety and efficacy of 16 weeks of telaprevir and boceprevir in well-compensated cirrhotics. In the CUPIC study by week 16, 23% discontinued all treatment medications and 15% discontinued due to adverse events.²⁷ In an updated analysis from the International Liver Congress Meeting in Amsterdam 2013, 47% of patients discontinued prematurely and 21% discontinued due to severe adverse events.²⁸ Our results support the results in the CUPIC trial. Our results are remarkably similar in that 52% discontinued treatment early and 22% discontinued due to adverse events. In addition, results from our multivariable analysis echo similar conclusions by Hezode *et al.* In both studies, low platelets were associated with discontinuation due to an adverse event, and older age and lower baseline haemoglobin were associated with anaemia.

In summary, our data show that there were few differences in the side-effect profile of triple therapy between patients with advanced fibrosis or cirrhosis and those without. Despite the lack of difference found between patients with and without advanced fibrosis or cirrhosis, the rate of adverse events was still high. Providers must be vigilant in monitoring for safety in all patients treated with telaprevir. Our findings may help practitioners increase the safety of HCV treatment by increasing awareness of potential risk factors for development of adverse events. Our study group represents the composition of the HCV-infected population as it may appear in the future.²⁹ Older and female patients with low platelet counts may experience more severe side effects of triple therapy, suggesting that closer monitoring of these patients may be prudent. We also observed four decompensation events in three patients with advanced fibrosis. Until new and safer drugs for treatment of genotype-1 hepatitis C become available for clinical use, more information about the effects of race and fibrosis stage on the tolerability and outcome of therapy is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med.* 2006; 144:705–14. [PubMed: 16702586]
2. Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl.* 2003; 9:331–8. [PubMed: 12682882]
3. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med.* 2009; 360:1827–38. [PubMed: 19403902]
4. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology.* 2011; 54:1433–44. [PubMed: 21898493]
5. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med.* 2011; 364:2405–16. [PubMed: 21696307]
6. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med.* 2011; 364:2417–28. [PubMed: 21696308]
7. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med.* 2011; 364:1207–17. [PubMed: 21449784]
8. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med.* 2011; 364:1195–206. [PubMed: 21449783]
9. Feuerstadt P, Bunim AL, Garcia H, et al. Effectiveness of hepatitis C treatment with pegylated interferon and ribavirin in urban minority patients. *Hepatology.* 2010; 51:1137–43. [PubMed: 20049907]
10. Ghosal A, Yuan Y, Tong W, et al. Characterization of human liver enzymes involved in the biotransformation of boceprevir, a hepatitis C virus protease inhibitor. *Drug Metab Dispos.* 2011; 39:510–21. [PubMed: 21123164]
11. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology.* 2006; 43:1317–25. [PubMed: 16729309]
12. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology.* 2007; 46:32–6. [PubMed: 17567829]
13. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med.* 2000; 342:1878–86. [PubMed: 10861324]
14. Hu CC, Lin CL, Kuo YL, et al. Efficacy and safety of ribavirin plus pegylated interferon alfa in geriatric patients with chronic hepatitis C. *Aliment Pharmacol Ther.* 2013; 37:81–90. [PubMed: 23121150]
15. Chayama K, Hayes CN, Abe H, et al. IL28B but not ITPA polymorphism is predictive of response to pegylated interferon, ribavirin, and telaprevir triple therapy in patients with genotype 1 hepatitis C. *J Infect Dis.* 2011; 204:84–93. [PubMed: 21628662]
16. Serfaty L, Forns X, Goeser T, et al. Insulin resistance and response to telaprevir plus peginterferon alpha and ribavirin in treatment-naïve patients infected with HCV genotype 1. *Gut.* 2012; 61:1473–80. [PubMed: 22387529]
17. Butt AA, Umbleja T, Andersen JW, Chung RT, Sherman KE. The incidence, predictors and management of anaemia and its association with virological response in HCV/HIV coinfecting persons treated with long-term pegylated interferon alfa 2a and ribavirin. *Aliment Pharmacol Ther.* 2011; 33:1234–44. [PubMed: 21535051]
18. Canonico PG, Kastello MD, Spears CT, Brown JR, Jackson EA, Jenkins DE. Effects of ribavirin on red blood cells. *Toxicol Appl Pharmacol.* 1984; 74:155–62. [PubMed: 6740666]
19. De Franceschi L, Fattovich G, Turrini F, et al. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology.* 2000; 31:997–1004. [PubMed: 10733558]

20. Sulkowski MS, Wasserman R, Brooks L, Ball L, Gish R. Changes in haemoglobin during interferon alpha-2b plus ribavirin combination therapy for chronic hepatitis C virus infection. *J Viral Hepatitis*. 2004; 11:243–50.
21. Yoneyama K, Miyagishi K, Kiuchi Y, Shibata M, Mitamura K. Risk factors for infections in cirrhotic patients with and without hepatocellular carcinoma. *J Gastroenterol*. 2002; 37:1028–34. [PubMed: 12522534]
22. O’Keefe SJ, El-Zayadi AR, Carraher TE, Davis M, Williams R. Malnutrition and immuno-incompetence in patients with liver disease. *Lancet*. 1980; 2:615–7. [PubMed: 6107408]
23. Brennan BJ, Morcos PN, Wang K, et al. The pharmacokinetics of peginterferon alfa-2a and ribavirin in African American, Hispanic and Caucasian patients with chronic hepatitis C. *Aliment Pharmacol Ther*. 2012; 35:1209–20. [PubMed: 22469033]
24. Srivastava S, Bertagnoli M, Lewis JH. Sustained virological response rate to pegylated interferon plus ribavirin for chronic hepatitis C in African Americans: results in treatment-naïve patients in a university liver clinic. *J Natl Med Assoc*. 2005; 97:1703–7. [PubMed: 16396063]
25. Conjeevaram HS, Fried MW, Jeffers LJ, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology*. 2006; 131:470–7. [PubMed: 16890601]
26. Hepburn MJ, Hepburn LM, Cantu NS, Lapeer MG, Lawitz EJ. Differences in treatment outcome for hepatitis C among ethnic groups. *Am J Med*. 2004; 117:163–8. [PubMed: 15276594]
27. Hezode C, Fontaine H, Dorival C, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J Hepatol*. 2013; 59:434–41. [PubMed: 23669289]
28. Fontaine H, Hezode C, Dorival C, et al. 60 SVR12 rates and safety of triple therapy including telaprevir or boceprevir in 221 cirrhotic non responders treated in the French Early Access Program (ANRS CO20-CUPIC). *J Hepatol*. 2013; 58:S27.
29. Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology*. 2013; 57:2164–70. [PubMed: 23280550]

Table 1

Baseline patient characteristics by fibrosis stage

Characteristics	F0–F2	F3–F4	P value
<i>n</i> (%)	103 (59%)	71 (41%)	–
Age, year median (IQR)	56 (52–61)	60 (55 – 63)	0.01 *
BMI, kg/m ²	27.0 (24.7–30.0)	27.0 (25.0–30.9)	0.77 [†]
Weight, kg	77.3 (68.2–90.5)	80.9 (72.7–89.5)	0.58 [†]
RBV dose-to-weight ratio, mg/kg	13.9 (12.4–15.3)	13.6 (12.7–15.3)	0.74 [†]
Male, <i>n</i> (%)	60 (58%)	48 (68%)	0.27 [§]
Black race, <i>n</i> (%)	30 (29%)	11 (15%)	0.02 [§]
Hispanic, <i>n</i> (%)	33 (32%)	26 (37%)	0.63 [§]
Prior treatment history			
Naïve	32 (31%)	24 (34%)	0.90 [‡]
Relapser	22 (21%)	11 (16%)	
Nonresponder	43 (42%)	32 (45%)	
Intolerant	4 (4%)	3 (4%)	
Unknown	2 (2%)	1 (1%)	
Diabetes, <i>n</i> (%)	14 (14%)	17 (24%)	0.11 [§]
HCV RNA, log(HCV RNA)	6.51 (6.05–6.89)	6.36 (6.01–6.74)	0.21 *
Creatinine, mg/dL	0.97 (0.80–1.00)	0.92 (0.80–1.00)	0.91 *
Haemoglobin, g/dL	14.2 (13.3–15.3)	14.0 (12.9–15)	0.17 [†]
INR	1 (1.00–1.00)	1 (1.00–1.20)	<0.01 [†]
Total Bilirubin, mg/dL	0.5 (0.40–0.83)	0.8 (0.50–1.00)	<0.01 [†]
Platelets, ×10 ³ /μL	193 (154–224)	109 (73–159)	<0.01 [†]
ALT, U/L	59 (42–95)	86 (60–114)	<0.01 [†]
AST, U/L	50 (35–82)	80 (54–120)	<0.01 [†]
Baseline FIB-4	2.23 (1.48–2.74)	5.24 (3.11–7.60)	<0.01 [†]

* T-test;

[†] Mann–Whitney;[‡] Chi-square;[§] Fisher exact.

Table 2

Logistic regression for complete discontinuation due to an adverse event

	Univariable		Fully adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, per year	1.05 (0.99–1.10)	0.07	1.12 (1.03–1.23)	0.01
Gender, female	1.36 (0.66–2.79)	0.41	7791.69 (9.09–6 675 822.19)	0.01
Age*Gender interaction	–	–	0.87 (0.77–0.97)	0.01
Race, black	1.16 (0.51–2.64)	0.73	1.84 (0.73–4.65)	0.20
Treatment history, nonresponder/intolerant	0.99 (0.49–2.03)	0.99	0.78 (0.36–1.73)	0.55
% normal haemoglobin, per%	0.99 (0.97–1.04)	0.96	0.99 (0.96–1.03)	0.72
Log (HCV viral load)	1.07 (0.63–1.82)	0.81	1.06 (0.6–1.87)	0.85
Platelets, per 10 ³ /μL	0.99 (0.98–1.00)	0.04	0.99 (0.98–1.00)	0.03
F3–F4 fibrosis	1.73 (0.85–3.55)	0.13	1.74 (0.79–3.85)	0.17