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Telaprevir or boceprevir in treatment-experienced cirrhotics: virological results of the CUPIC cohort (ANRS CO20)

Short title: Triple therapy in HCV genotype 1 cirrhotics

CHRISTOPHE HEZODE[1*], HELENE FONTAINE[2*], CELINE DORIVAL[3], FABIEN ZOULIM[4], DOMINIQUE LARREY[5], VALERIE CANVA[6], VICTOR DE LEDINGHEN[7], THIERRY POYNARD[8], DIDIER SAMUEL[9], MARC BOURLIERE[10], LAURENT ALRIC[11], JEAN-JACQUES RAABE[12], JEAN-PIERRE ZARSKI[13], PATRICK MARCELLIN[14], GHASSAN RIACHI[15], PIERRE-HENRI BERNARD[16], VERONIQUE LOUSTAUD-RATTI[17], OLIVIER CHAZOUILLERES[18], ARMAND ABERGEL[19], DOMINIQUE GUYADER[20], SOPHIE METIVIER[21], ALBERT TRAN[22], VINCENT DI MARTINO[23], XAVIER CAUSSE[24], THONG DAO[25], DAMIEN LUCIDARME[26], ISABELLE PORTAL[27], PATRICE CACOUB[28], JEROME GOURNAY[29], VERONIQUE GRANDO-LEMAIRE[30], PATRICK HILLON[31], PIERRE ATTALI[32], THIERRY FONTANGES[33], ISABELLE ROSA[34], VENTZISLAVA PETROV-SANCHEZ[35], YOANN BARTHE[3], JEAN-MICHEL PAWLOTSKY[36], STANISLAS POL[2], FABRICE CARRAT[3,37], JEAN-PIERRE BRONOWICKI[38], AND THE CUPIC STUDY GROUP[**].

[1]Department of Hepatology and Gastroenterology, Hôpital Henri Mondor, AP-HP, Université Paris-Est, INSERM U955, Créteil, France; [2]Department of Hepatology, Hôpital Cochin, APHP, Université Paris-René Descartes, INSERM U1016, Paris, France; [3]INSERM UMR-S 1136, Université Pierre et Marie Curie Paris 6, Paris, France; [4]Department of Hepatology, Hospices Civils de Lyon, INSERM U1052, Université de Lyon, Lyon, France; [5]Liver unit-

IRB-INSERM1040, Hôpital Saint Eloi, Montpellier, France; [6]Department of Hepatology and Gastroenterology, Centre Hospitalier Régional et Universitaire Claude Huriez, Lille, France; [7]Department of Hepatology and Gastroenterology, Hôpital Haut-Lévêque, Pessac, INSERM U1053, Université Bordeaux Segalen, Bordeaux, France; [8]Department of Hepatology and Gastroenterology, Groupe Hospitalier Pitié-Salpétrière, AP-HP, Université Pierre et Marie Curie Paris 6, INSERM UMR-S938, Paris, France; [9]Centre Hépato-Biliaire, Hôpital Paul Brousse, AP-HP, UMR-S785, Université Paris-Sud, INSERM U785, Villejuif, France; [10]Department of Hepatology and Gastroenterology, Hôpital Saint Joseph, Marseille, France; [11]Department of Internal Medicine and Digestive Diseases, UMR-152, Toulouse III University, France; [12]Department of Hepatology and Gastroenterology, Centre Hospitalier Régional, Metz, France; [13]Department of Hepatology and Gastroenterology, Centre Hospitalo-Universitaire, INSERM U823, Grenoble, France; [14]Department of Hepatology, Hôpital Beaujon, AP-HP, Université Paris-Diderot, INSERM CRB3, Clichy, France; [15]Department of Hepatology and Gastroenterology, CHU Charles Nicolle, Rouen, France; [16]Service d'Hépatologie et Gastroentérologie, Hôpital Saint-André, Bordeaux, INSERM U1053, Université Bordeaux Segalen, Bordeaux, France; [17]Department of Hepatology and Gastroenterology, CHU Dupuytren, Université de Limoges, UMR INSERM U1092, Limoges, France; [18]Department of Hepatology, Hôpital Saint-Antoine, AP-HP, Paris, France; [19]Department of Hepatology and Gastroenterology, CHU Estaing, Université d'Auvergne, UMR 6284, Clermont-Ferrand, France; [20]Service des Maladies du Foie, CHU Rennes, Université de Rennes 1, INSERM U991, Rennes, France; [21]Department of Hepatology and Gastroenterology, CHU Purpan, Toulouse, France; [22]Digestive Center, Centre Hospitalier Universitaire de Nice, INSERM U1065-8, Nice, France; [23]Service d'Hépatologie, CHU Jean Minjoz, Université de Franche Comté, Besançon, France; [24]Department of Hepatology and Gastroenterology and Digestive Oncology, CHR La Source, Orléans, France; [25]Department of

Hepatology and Gastroenterology, CHU, INSERM U1075, Caen, France; [26]Department of Hepatology and Gastroenterology, Groupe Hospitalier de l'Institut Catholique Lillois, Faculté Libre de Médecine, Lille, France; [27]Department of Hepatology and Gastroenterology, Hôpital de la Conception, Marseille, France ; [28]Department of Internal Medicine, Groupe Hospitalier Pitié-Salpêtrière, AP-HP, Université Pierre et Marie Curie Paris 6, INSERM, UMR-S959, CNRS, UMR 7211, Paris, France; [29]Department of Hepatology and Gastroenterology, Hôpital Hôtel-Dieu, Nantes, France; [30]Department of Hepatology and Gastroenterology, Hôpital Jean Verdier, AP-HP, Université Paris 13, Bondy, France; [31]Department of Hepatology and Gastroenterology, CHU de Dijon, Université de Bourgogne, Dijon, France; [32]Department of Hepatology and Gastroenterology, Hôpital de Bicêtre, AP-HP, Le Kremlin-Bicêtre, France; [33]Department of Hepatology and Gastroenterology, Hôpital P Oudot, Bourgoin-Jallieu, France ; [34]Department of Hepatology and Gastroenterology, Centre Hospitalier Intercommunal, Créteil, France; [35]Unit for Basic and Clinical research on viral hepatitis, French National Agency for research on Aids and viral Hepatitis, Paris, France; [36]National Reference Center for Viral Hepatitis B, C and Delta, Department of Virology, Hôpital Henri Mondor, AP-HP, Université Paris-Est, INSERM U955, Créteil, France; [37]Department of public health, Hôpital Saint-Antoine, AP-HP, Paris, France; [38]Department of Hepatology and Gastroenterology, Centre Hospitalier Universitaire de Nancy, Université de Lorraine, INSERM U954, Vandoeuvre-les-Nancy, France.

*These two authors equally contributed to the work

**Additional CUPIC investigators are listed in the Supplementary Appendix.

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Abbreviations

ANRS: Agence Nationale de Recherches sur le SIDA et les Hépatites Virales

BOC: boceprevir

CUPIC: compassionate use of protease inhibitors in viral C cirrhosis

HCV: hepatitis C virus

HIV: human immunodeficiency virus

ITT: intent-to-treat

Peg-IFN: pegylated interferon

PI: protease inhibitor

RBV: ribavirin

SAE: serious adverse event

SVR: sustained virological response

TVR: telaprevir

Correspondence:

Prof. Jean-Pierre Bronowicki,

INSERM U954, Centre Hospitalier Universitaire de Nancy, Université de Lorraine, Vandoeuvre-les-Nancy, France

Tel: +33 383153355

Fax: +33 383153633

E-mail: jp.bronowicki@chu-nancy.fr

Disclosures:

- Christophe Hézode has been a clinical investigator, speaker and/or consultant for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche.

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- Dominique Larrey has been a clinical investigator, speaker and/or consultant for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche.

- Valérie Canva has been a clinical investigator and/or speaker for Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche.

- Victor de Ledinghen has been a clinical investigator, speaker and/or consultant for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Echosens, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche.

- Thierry Poynard has been a clinical investigator, speaker and/or consultant for Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, and Merck Sharp & Dohme.

- Didier Samuel has been consultant for Astellas, Biotest, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, LFB, Merck Sharp & Dohme, Novartis, and Roche.

- Marc Bourlière has been a clinical investigator, speaker and/or consultant for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GSK, Janssen Pharmaceuticals, Merck Sharp & Dohme, Roche, and Vertex.

- Laurent Alric has been a clinical investigator, speaker and/or consultant for Bristol-Myers Squibb, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche.

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- Jean-Pierre Zarski has been speaker and/or consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, Roche, and Siemens.

- Patrick Marcellin has been clinical investigator, speaker and/or consultant for Abbvie, Alios BioPharm, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Vertex pharmaceuticals.

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- Olivier Chazouilleres has been clinical investigator, speaker and/or consultant for Aptalis, Echosens, Gilead Sciences, Mayoly-Spindler and Roche.

- Armand Abergel has been clinical investigator, speaker and/or consultant for Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche.

- Dominique Guyader has been a clinical investigator, speaker and/or consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche.

- Sophie Métivier has nothing to disclose.

- Albert Tran has been a clinical investigator for Janssen Pharmaceuticals, and Merck Sharp & Dohme.

- Vincent Di Martino has been a clinical investigator, speaker and/or consultant for Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and Roche.

- Xavier Causse has been consultant for Janssen Pharmaceuticals, and Merck Sharp & Dohme.

- Thong Dao has been consultant for Gilead Sciences, and Merck Sharp & Dohme.

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- Véronique Grando-Lemaire has nothing to disclose.

- Patrick Hillon has been a clinical investigator, speaker and/or consultant for Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche.

- Pierre Attali has been a clinical investigator for Boehringer Ingelheim, Bristol-Myers Squibb, Cytheris, Gilead Sciences, and Novartis.

- Thierry Fontanges has been speaker and/or consultant for Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, and Merck Sharp & Dohme.

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- Fabrice Carrat has nothing to disclose.

- Jean-Pierre Bronowicki has been a clinical investigator, speaker and/or consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, Novartis and Roche.

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ABSTRACT

Background and aims: The efficacy of peginterferon/ribavirin with boceprevir or telaprevir was evaluated in a limited number of selected treatment-experienced cirrhotics with HCV genotype 1 infection.

Methods: 511 patients with compensated cirrhosis due to HCV genotype 1 who did not respond to a prior course of peginterferon/ribavirin were treated for 48 weeks with either telaprevir or boceprevir in the framework of the French Early Access Programme (CUPIC cohort). **The distribution was the following**: 44.3% of relapsers or patients with breakthrough, 44.8% of partial responders and 8.0% of null responders. Virological efficacy (SVR12) and safety were assessed. **This was an observational study which did not allow a head-to-head comparison between the 2 treatment regimens.**

Results: 299 and 212 patients received telaprevir and boceprevir, respectively. With telaprevir, the SVR12 was 74.2% in relapsers, 40.0% in partial responders and 19.4% in null responders. With boceprevir, the SVR12 was 53.9%, 38.3% and 0% in the same groups, respectively. In multivariate analysis, the SVR12 predictors were the prior treatment response, no lead-in phase, the HCV subtype and the baseline platelet count. Severe adverse events occurred in 49.9% of cases, including liver decompensation or severe infections in 10.4% and death in 2.2%. In multivariate analysis, the baseline albumin level and platelet count were the two predictors of severe side effects or death.

Conclusions: Relatively high SVR rates can be achieved with a triple combination including telaprevir or boceprevir in real-life non-responders with compensated cirrhosis, at the cost of frequent, often severe side effects. Baseline albumin level and platelet count are useful in guiding treatment decisions.

ClinicalTrials.gov number, NCT01514890.

Key-words: chronic hepatitis C, cirrhosis, boceprevir, telaprevir.

Introduction

Two direct-acting antiviral drugs, telaprevir (TVR) and boceprevir (BOC), both hepatitis C virus (HCV) non-structural 3-4A protease inhibitors (PIs), were recently approved in combination with pegylated interferon (Peg-IFN) and ribavirin (RBV) for the treatment of chronic HCV genotype 1 infection (1-4). Phase 3 trials showed significantly improved sustained virological response (SVR) rates compared with Peg-IFN/RBV alone in both treatment-naïve and treatment-experienced patients (1-4). However, the gain in efficacy was associated with an increased frequency of side effects, including a 20% incremental anaemia with both PIs, dysgeusia with BOC, and frequent skin and gastrointestinal disorders with TVR (1-4). Patients with cirrhosis have the greatest need for antiviral treatment given the higher survival rates in those who achieve an SVR compared with non-responders, as a result of less frequent liver failure and hepatocellular carcinoma (5-12). These patients are considered difficult-to-treat due to both a lower SVR rate than in non-cirrhotics and an increased risk of therapy. However, the administration of Peg-IFN/RBV in patients with compensated cirrhosis has proven to be feasible (1-4, 13-16). This patient population is generally under-represented in registration clinical trials, and the cirrhotics included in these studies are highly selected and do not reflect well the actual population of HCV-infected cirrhotics who are potential candidates for direct-acting antiviral–based regimens.

The French “Autorisation Temporaire d’Utilisation” (temporary authorization for use) is an early access programme that gives patients access to a medicinal product before it is granted a marketing authorization. Patients with compensated cirrhosis who were relapsers or partial responders to a prior course of Peg-IFN/RBV were treated prior to approval of TVR and BOC within the framework of this programme, beginning in January 2011. Null responders were subsequently given access to these therapies when the drugs were approved.

The ANRS CO20 “Compassionate Use of Protease Inhibitors in viral C Cirrhosis” (CUPIC) study is a cohort study sponsored by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) that enrolled patients benefiting from the temporary authorization for use early access programme in selected centres. The objective of this cohort study was to evaluate the efficacy and safety of triple combination regimens including TVR or BOC in treatment-experienced cirrhotic patients in the real-life setting. This article presents the week 60 efficacy (including SVR12) and safety results of this study.

Patients and methods

Patients

The ANRS CO20-CUPIC cohort is a national multicentre prospective cohort study conducted in 56 French centres (ClinicalTrials.gov number NCT01514890). From February 2011 to April 2012, patients with compensated cirrhosis (Child-Pugh class A) chronically infected with HCV genotype 1 who failed on a prior course of IFN with or without RBV and started triple combination therapy in the French Early Access Programme in the participating centres were included. Initially, only relapsers (or patients with a virological breakthrough) and partial responders were included in the Early Access Programme and recruited in the cohort. Null responders started to be included in the cohort study after the approval of both PIs in September 2011. (Supplementary materials).

In all instances, the diagnosis of cirrhosis was confirmed by a liver biopsy or a non-invasive test (e.g. Fibrotest®, Fibroscan®, Fibrometer® or Hepascore®) at the investigator's discretion, according to the French recommendations (17). The non-inclusion criteria were an HIV and/or hepatitis B virus co-infection, renal insufficiency (defined by creatinine clearance <50 mL/min), an organ graft, and contraindication to the use of interferon.

Written informed consent was obtained from each patient before enrolment. The protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the "Ile de France IX" Ethics Committee (Créteil, France).

Objectives

The goals of the study were to evaluate the virological response defined as undetectable HCV RNA 12 weeks after treatment discontinuation (SVR12) based on the Food and Drug Administration recommendations and its safety over the full duration of treatment.

Treatments

The choice between a TVR- or BOC-based regimen **and the use of a lead-in were** was at the investigator's discretion. The patients were not randomized; thus the study did not allow for comparisons between the two treatment regimens. The treatment schedules and recommended stopping rules are described in the Supplementary materials.

HCV RNA level monitoring

HCV RNA levels were measured at baseline and at weeks 4, 8, 12, 16, 24, 36, and 48 of therapy, and 12 and 24 weeks after its withdrawal, with a real-time PCR-based assay, either COBAS AmpliPrep®/COBAS TaqMan® (Roche Molecular Systems, Pleasanton, California) with a lower limit of detection of 15 IU/mL, or $m2000_{SP}$/$m2000_{RT}$ (Abbott Molecular, Des Plaines, Illinois), with a lower limit of detection of 12 IU/mL. Both assays have been validated for their accuracy in patients infected with HCV genotype 1 (18-19).

Safety assessments

The safety profile assessment is described in the Supplementary materials. Data on all adverse events were collected until the 60^{th} week of follow-up. The definition of clinical and laboratory grade 3 or 4 adverse events, serious adverse event (SAE) and serious cutaneous adverse reaction (20) are described in the Supplementary materials. The factors associated with severe complications of cirrhosis (infection, hepatic decompensation) or death were explored. In addition, the factors associated with grade 3 or 4 anaemia or blood transfusion were also analyzed. The management of anaemia (RBV dose reductions and/or erythropoietin administration, authorized in France when the haemoglobin level is below 10 g/dL, and/or blood transfusion) was at the investigator's discretion. Use of other hematopoietic growth factors for neutropenia or thrombocytopenia was also recorded.

Statistical analysis

We estimated that 900 patients would be needed for the cohort to have a 3% precision in estimating the SVR. The efficacy and safety interim analysis was not pre-specified in the protocol, but decided by the Scientific Committee in February 2012 based on preliminary reports of safety findings. Therefore, no sample size was pre-defined. All patients who reached week 60 of follow-up by March 1, 2013 were included in the present analysis.

Early virological breakthrough was defined as an undetectable HCV RNA before week 12 of triple therapy with detectable HCV RNA at week 12; late virological breakthrough as an undetectable HCV RNA after week 12 with detectable HCV RNA at week 48; relapse as an undetectable HCV RNA at week 48 with detectable HCV RNA at week 60 (i.e. week 12 post-treatment); non-response as persistently detectable HCV RNA during treatment; and SVR12 as an undetectable HCV RNA at week 60, i.e. 12 weeks after the end of therapy. Patients with detectable HCV RNA at week 12 had to stop therapy, according to the pre-defined stopping rules. Efficacy and safety analyses were performed on an intent-to-treat basis. Missing HCV RNA values at week 12 post-therapy were considered as treatment failures. Missing intermediate HCV RNA values were considered as undetectable when the preceding and subsequent HCV RNA levels were undetectable, and detectable otherwise. Blood parameters were categorized according to thresholds used to define eligibility in a recently published randomized trial of PI-based triple therapy (2).

Comparisons between independent groups used the Mann-Whitney test for continuous variables or Fisher's exact test for categorical variables; and within-group comparisons were made using the Wilcoxon signed-rank test for continuous variables or McNemar's Chi square tests for categorical variables. Logistic regression models were used to identify predictors of SVR12, severe complications and grade 3/4 anaemia or blood transfusion. For

each tested covariate, a univariate model was estimated. Covariates with p values <.05 in likelihood ratio testing in univariate analysis were included in a multivariate model, and selection of independent covariates was based on a backward elimination procedure, retaining covariates with p values <.05.

All statistical computations were performed using SAS software version 9.3 (SAS Institute Inc, Cary, North Carolina).

All authors had access to the study data and had reviewed and approved the final manuscript.

Results

Baseline demographics and disease characteristics

Six hundred and sixty patients over 18 years of age were enrolled in 56 centres; 511 patients reached week 60 of follow-up and were thus included in this analysis, including 299 treated with TVR and 212 with BOC. The baseline demographics and disease characteristics are shown in Table 1. Of the 511 patients, 346 (67.7%) were men, and their mean age was 57.0±9.7 years. The prior treatment response was a relapse or a virological breakthrough in 226 cases (44.3%, including 17 patients with a virological breakthrough), a partial response in 229 cases (44.8%), a null response in 41 cases (8.0%) and undetermined in the remaining 15 cases (2.9%). At baseline, cirrhosis was compensated and classified as Child-Pugh A in 483 patients (94.5%), and the MELD score, available in 460 patients (90.0%), was <13 in 433 of them (94.1%). The mean albumin level was 40.2±4.9 g/dL and the mean platelet count was 148,000±67,000/mm^3. When considering age and laboratory parameters, at least one exclusion criterion from the phase III studies in treatment-experienced patients (e.g. REALIZE and RESPOND-2) (2,4) was reported in 164 (32.1%) and 227 (44.4%) patients treated with TVR and BOC, respectively. The patients were infected with HCV subtype 1b in 52.8% of cases and 62.6% of them had a baseline HCV RNA level ≥800,000 IU/mL. The mean treatment duration was 49.0±26.4 weeks with TVR and 46.4±26.8 weeks with BOC. The mean duration of PI use was 11.0±2.5 weeks with TVR and 32.4±15.1 weeks with BOC.

Efficacy of triple therapy including TVR

The intent-to-treat (ITT) efficacy analysis in the 299 patients who received TVR is shown in Figure 1A. The primary endpoint, ie, SVR12, was achieved in 92/124 (74.2%) patients with a relapse or a virological breakthrough (89/117, 76.1% and 3/7, 42.9%, respectively), 54/135

partial responders (40.0%), 6/31 null responders (19.4%) and 3/9 undetermined patients, p<0.0001.

Among the 155 patients who achieved an SVR (all groups together), 33 (21.3%) had to discontinue treatment prematurely, including 8 before and 25 after week 12. **The use of a lead-in was at the investigator's discretion.** Forty-five patients receiving TVR were treated with a lead-in phase: their SVR12 rate was lower than in those treated without a lead-in phase (15/45, 33.3% *versus* 140/254, 55.1%; p=0.0092). Patients treated with a lead-in were older (59.5 vs 56.7 years, p=0.036) and experienced more adverse events leading to premature treatment discontinuation: 35.6% (16/45) *versus* 23.8% (55/254) in the patients without lead-in (p=0.0564).

The SVR12 rate was significantly higher in patients infected with HCV subtype 1b than 1a: 61.4% (102/166) *versus* 34.3% (35/102); p<0.0001) (Figure 1B). The difference was not significant between patients with more or less than 800,000 IU/mL of HCV RNA at baseline: 48.7% (90/185) *versus* 57.5% (65/113); p=0.1219. The patients who achieved a rapid virological response (undetectable HCV RNA at treatment week 4 or at treatment week 8 in case of lead-in) were more likely to achieve an SVR: 63.1% (125/198) *versus* 29.7% (30/101); p<0.0001 (Figure 1C).

Among the 144 patients who failed on triple combination therapy, 37 met the stopping rule criteria, including 6 (2.0% of the 299 treated patients) who experienced an early virological breakthrough and 31 (10.4%) who did not respond. A late virological breakthrough was observed after discontinuing TVR in 49 patients (16.4%), a relapse in 44 patients (14.7%) and 14 patients (4.7%) failed due to other reasons, including loss to follow-up (7), death (4), or missing HCV RNA level measurements (3).

Efficacy of triple therapy including BOC

The intent-to-treat (ITT) efficacy analysis in the 212 patients who received BOC is shown in Figure 2A. The primary endpoint, ie, SVR12, was achieved in 55/102 (53.9%) patients with a relapse or a virological breakthrough (50/92, 54.3% and 5/10, 50%, respectively), 36/94 partial responders (38.3%), 0/10 (0%) null responders, and none of the undetermined patients, p=0.0004.

Among the 91 patients who achieved an SVR (all groups together), 12 (13.2%) had to discontinue treatment prematurely, including 2 before and 10 after week 16, i.e. lead-in plus 12 weeks of BOC.

The SVR rate was significantly higher in patients infected with HCV subtype 1b than 1a: 52.9% (55/104) *versus* 33.3% (29/87); p=0.0084 (Figure 2B). The difference was not significant between patients with more or less than 800,000 IU/mL of HCV RNA at baseline: 43.7% (59/135) *versus* 41.7% (30/72); p=0.8829. Higher SVR rates were observed in patients who exhibited a $\geq$1 $\log_{10}$ decline of HCV RNA level from baseline at treatment week 4 (end of lead-in) than in those who did not: 62.6% (62/99) *versus* 25.7% (29/113); p<0.0001 (Figure 2C). The SVR12 was also significantly more frequent in patients with undetectable HCV RNA at treatment week 8 (week 4 of BOC administration): 71.6% (58/81) *versus* 25.2% (33/131); p<0.0001 (Figure 2C), and in patients who exhibited a $\geq$3 $\log_{10}$ decline of HCV RNA level from baseline or had undetectable HCV RNA at treatment week 8: 58.4% (87/149) *versus* 6.3% (4/63); p<0.0001.

Among the 121 patients who failed on triple combination therapy, 62 (29.2% of the 212 treated patients) did not respond. A virological breakthrough was observed after discontinuing BOC in 19 patients (9.0%), a relapse in 36 patients (17.0%) and 4 patients (1.9%) failed due to other reasons, including death (2), or missing HCV RNA level measurements (2).

Independent predictors of SVR12

Patients from the TVR and BOC groups were pooled to identify factors related to the SVR12. The results of the univariate analysis are shown in Table 2. Four independent factors predicting the SVR12 were identified: the prior treatment response, including relapse or breakthrough (odds ratio [OR]=2.96, 95% CI: 1.97-4.44, p<0.0001) and null response (OR=0.28, 95% CI: 0.11-0.73, p=0.0086) *versus* partial response; no lead-in phase (OR=1.78, 95% CI: 1.20-2.66, p=0.0044); a platelet count >100,000/mm^3 (OR=2.15, 95% CI: 1.34-3.45, p=0.0015); and an HCV subtype 1b (OR=2.50, 95% CI: 1.62-3.85, p<0.0001) *versus* subtype 1a. A nearly significant trend was noted with serum albumin ≥35g/L (OR=1.86, 95% CI: 0.97- 3.56, p=0.0614).

Safety

Tables 3 and 4 show the safety profiles of the triple therapies including TVR or BOC, respectively. A high incidence of SAEs (n=850) was observed during the 60 weeks of follow-up. SAEs occurred in 255 patients (49.9%), leading to early discontinuation of all drugs in 108 (21.1%). **The probability of remaining free of any serious adverse event is represented in the supplementary materials (Figures 1 and 2).**

Deaths occurred in 11 patients (2.2%) during the course of therapy, mainly related to severe infections: septicaemia (n=4), pneumonia (n=3), endocarditis (n=1). Other causes of death were hepatic decompensation related to variceal bleeding (n=2) and massive bleeding due to an aortic aneurysm (n=1). Death occurred after a median time of 20 weeks and two deaths occurred during the lead-in phase, i.e. without PI.

Apart from death, severe complications, including severe infections and hepatic decompensation, occurred in 43 patients (8.4%). Severe infections were reported in 28 patients (5.5%), including pneumonia (n=5), septicaemia (n=5), acute pyelonephritis (n=3), cutaneous infection (n=4), acute cholecystitis (n=2), infectious diarrhoea (n=2), endocarditis

(n=1), ascites infection (n=1), and others (n=5). These infectious complications occurred after a median duration of antiviral treatment of 13.9 weeks (range: 2.3 to 47.3 weeks) and during the lead-in phase in one patient. The peg-IFN dose was reduced or discontinued in 10 patients (35.7%) before the occurrence of severe infection, and in an additional 16 patients (57.1%) after the onset of severe infection. In addition, episodes of hepatic decompensation (without death or infection) were observed in 15 patients (3.1%): ascites in 14 (93.3%), encephalopathy in 1 (6.7%).

Overall, 54 patients (10.6%) experienced severe complications or death. **Nearly one half of these severe complications occurred during the first 12 or 16 (in the case of lead-in) weeks, independently of treatment regimens (18/38 in the TVR cohort and 8/16 in the BOC cohort). Age per 10-year increase (OR= 1.61, 95% CI 1.13-2.30, p=0.0087), baseline serum albumin <35 g/L (OR=5.43, 95% CI: 2.72-10.83, p<0.0001) and baseline platelet count ≤100,000/mm^3 (OR=3.57, 95% CI: 1.81-7.02, p=0.0002)** were independently associated with death or severe infection or hepatic decompensation and a non-significant trend was noted with baseline haemoglobin level ≤12 g/dL for women, ≤13 g/dL for men **(OR=2.11, 95% CI: 0.96-4.63, p=0.0624). The probability of remaining free of severe complication or death is shown in the supplementary materials (Figures 3 and 4).**

The incidence of grade 2 anaemia (8.0 to ≤ 9.0 g/dL) was 22.9% (117/511). Grade 3-4 anaemia (haemoglobin ≤8.0 g/dL) occurred in 11.2% of cases (57/511). Out of 174 patients with anaemia, 168 (96.0%) received erythropoietin, the RBV dose was reduced or discontinued in 133 (76.4%), and blood transfusions were administered to 78 (44.8%) (Tables 3 and 4). Ninety-four patients (18.4%) experienced grade 3 or 4 anaemia and/or blood transfusion. **In multivariate analysis, the predictors of severe anaemia or blood transfusion were as follows: age per 10-year increase (OR = 2.08, 95% CI 1.56– 2.77, p <**

0.0001), baseline Hb ≤ 12 g/dL for females and ≤13 g/dL for males (OR = 4.30, 95% CI 2.21–8.37, p < 0.0001) and albumin <35 g/L (OR=1.95, 95% CI: 1.02-3.73, p=0.0448).

An increased creatinine level, defined as >80 µmol/L in women and >110 µmol/L in men, was observed during the treatment in the following percentages of patients: 1.04% at baseline, 4.6% after the first month of TVR (W4 or W8 in the case of lead-in), 6.6% at the end of TVR (W12 or W16 in the case of lead-in), 0% at W24 and 1% at the end of treatment (EOT) in the TVR cohort and 1.16% at baseline, 3.9% at W8, 5.8% at W16, 5.3% at W24 and 2.77 at EOT in the BOC cohort.

Risk/benefit ratio of triple therapy

Table 5 shows the SVR12 rates and the rates of death and severe complications according to the two baseline predictors of severe complications and death identified in the week 16 interim analysis, i.e. albumin level and platelet count (21).

Discussion

The CUPIC cohort is a large cohort of treatment-experienced cirrhotic patients infected with HCV genotype 1 treated with BOC or TVR in combination with peg-IFN and RBV in the real-life setting. Because the choice of TVR or BOC was made by the treating physicians and the patients were not randomized, no comparison can be made between the two PIs. However, our results provide, for each drug regimen, an accurate reflection of what can be expected in terms of antiviral efficacy and safety in this **particular** population with a clear indication for antiviral therapy, which was poorly documented in phase II and phase III trials. Altogether, our results demonstrate a substantial benefit of adding BOC or TVR to Peg-IFN and RBV in these patients, compared with the 0% to 10% global SVR rates in treatment-experienced cirrhotic patients retreated with Peg-IFN and RBV alone in phase III trials (2, 4).

The present study identifies baseline predictors of SVR12, including the prior treatment response, the absence of a lead-in phase, HCV subtype 1b, and a platelet count >100,000/mm^3, while a nearly significant trend was observed for serum albumin ≥35 g/L. These parameters can now be used in this population to guide treatment decisions and eventually to target therapy to those patients more likely to achieve high SVR rates.

Not surprisingly, the relapsers were the best candidates for triple therapy with BOC or TVR, with an SVR12 rate of 74.2% with TVR, a number in keeping with those reported in phase III trials. In contrast, the SVR12 rate was 53.9% with BOC, *versus* 83% in relapsers from the RESPOND-2 trial who received 48 weeks of treatment including 44 weeks of triple therapy. The difference could be explained by the small number of patients included in this trial compared with our cohort (18 *versus* 92 patients, respectively), and by the fact that patients with advanced fibrosis were pooled with cirrhotics in RESPOND-2 (22).

In the present study, the SVR12 rates in prior partial responders were of the order of 40%, in keeping with those reported in clinical trials in the same population (2, 4). In contrast, prior null responders rarely achieved an SVR12 (0% and 19.4% for BOC and TVR, respectively), suggesting that the approved triple therapy is not an appropriate therapeutic option in prior null responders with cirrhosis in the real-life setting. However, it is noteworthy that a small number of such patients were included. For BOC, data in prior null responders with cirrhosis are available in 3 patients in trials (23), and only 10 patients were included in our study. More patients (i.e. 31) were treated with TVR, and the observed SVR rate was of the same order as that reported in pooled non-cirrhotics and cirrhotics included in the REALIZE trial (14%) (16).

In the TVR cohort, the SVR12 rate was lower in patients who received a lead-in phase. This result was unexpected. In the REALIZE trial, which included a large number of patients in both groups, no significant SVR difference was observed between the patients randomized to have or not to have a lead-in phase, including the same three subgroups of prior response as those in the present study (4). The baseline characteristics **of our patients** were similar in the two groups, except that patients with a lead-in phase were older. Moreover, we observed more treatment discontinuation due to adverse events in patients who received a lead-in. This result might have been biased by the fact that physicians decided to start with a lead-in phase in patients who were less likely to respond and/or more likely to develop severe complications of therapy.

As already partly reported in our week 16 interim analysis (21), the safety profile over 60 weeks of follow-up was poor for both treatment regimens, and was characterized by a large number of SAEs and the occurrence of severe complications, such as severe infection or hepatic decompensation, and death in 10.6% of patients. **This may be explained in part by a greater mean age in our population compared with the phase III studies, and more**

severe liver disease with a relatively high rate of portal hypertension. The management of anaemia was at the investigator's discretion and involved erythropoietin prescription in most cases and RBV dose reduction more rarely. At the time of the study, clinicians were not convinced that anaemia could be managed first by RBV dose reduction without any impact on SVR. More recently, a prospective controlled trial has shown that RBV dose reduction can be the first strategy for anaemia management in treatment-naïve patients (24). However, it is worth noting that very few cirrhotic patients were included in this trial and that the SVR rate in cirrhotics was 57% in the "RBV dose reduction" arm *versus* 64% in the "erythropoietin" arm. So the validity of this strategy remains to be confirmed in treatment-experienced cirrhotic patients. As previously reported with Peg-IFN and RBV without PIs, one of the most frequent causes of severe infection was pneumonia (**25**). We did not investigate the effect of neutropenia and Peg-IFN dose reductions on the occurrence of these infections. However, vaccination against pneumococcus could be proposed before antiviral treatment. The number of patients was too small to evaluate the effect of this intervention. The other frequent cause of severe infection was septicaemia, raising the question of prophylactic antibiotic therapy during triple therapy in cirrhotic patients.

In five recent studies (including a meta-analysis) evaluating the natural history of cirrhotic patients with characteristics comparable to those from the CUPIC cohort, the annual incidence of deaths and/or liver decompensation varied from 6.2 to 11%, challenging the indication for triple therapy in this subgroup of patients (**26-30**). In the present analysis, two baseline parameters, the serum albumin level and platelet count, were found to be independent predictors of severe complications or death. Interestingly, these two parameters were also identified as strong predictors of SVR12 in our univariate analysis, although the association did not reach significance for albumin in the multivariate analysis when adjusted

for other factors. In order to assess the risk/benefit ratio of triple therapy better in the difficult-to-treat population of patients with compensated cirrhosis, we analyzed the SVR12 results with the two PIs according to baseline albumin level and platelet count. The subgroup of patients with both a low albumin level (<35 g/L) and a low platelet count (≤100,000/mm^3) at baseline represented 8.3% (37/448 patients) of the population with both predictors available. These patients had a high risk (51.4%) of severe complications and a low SVR12 rate (27%), raising the question as to whether these patients, who are the most in need of therapy, should be treated with **interferon-based** triple therapy. By contrast, we identified the subgroup of patients with albumin ≥35 g/L and platelet count >100,000/mm^3 as representing the majority of our population (68.3%), with a low risk of severe complications (6.2%) and a high SVR12 rate (54.9%). This result shows that triple therapy can be used confidently in this subgroup of patients. The remaining patients had an incidence of severe complications between 12.2% and 16.1% and a modest efficacy of triple therapy (29.0% to 36.5%). These patients could benefit from prophylaxis of treatment complications and should undergo careful monitoring while on therapy. Alternatively, most of them can wait for all-oral, IFN-free regimens. **The lack of a control group does not allow us to distinguish between severe events caused by treatment from those caused by the cirrhosis itself. However, the rate of observed severe events was much higher in this particular group of patient with advanced cirrhosis, low platelet count and low albumin level. Moreover, severe infection is a relatively rare event in non-treated compensated viral cirrhosis. Therefore, it's likely that the treatment contributed to these events.**

Recently, a new stopping rule has been proposed based on the on-treatment response at week 8, as a result of post-hoc analysis of the databases of 5 clinical trials including patients with advanced fibrosis or cirrhosis treated with BOC. In this analysis, none of the 22 patients with a less than 3 $\log_{10}$ HCV RNA decline from baseline achieved an SVR (**31**). Among our 63

patients with a less than 3 $\log_{10}$ decline in HCV RNA level at week 8, only 6.3% achieved an SVR12. This result suggests that discontinuing triple therapy should be considered at week 12 in these difficult-to-cure patients, especially if they tolerate treatment poorly.

In conclusion, the CUPIC cohort study, performed in the real-life setting of patients with compensated cirrhosis associated with HCV genotype 1 infection, provides useful clinical information for the management of triple therapy in this difficult-to-treat population. It demonstrates the potential benefits, but also emphasizes the risks, of treating such patients with these therapies. In practice, the risk of developing SAEs, including severe complications or death, should be carefully balanced against the likelihood of a virological response and subsequent improvement of survival. Based on our results, three baseline parameters should be considered to guide treatment decisions at the individual level. They include the prior treatment response (triple therapy is not an optimal option for prior null responders with cirrhosis), the serum albumin level and the platelet count (treatment-experienced patients with compensated cirrhosis with a platelet count ≤100,000 /mm^3 and serum albumin <35 g/L should not be treated with a triple combination). Relapsers and partial responders to a prior course of Peg-IFN/RBV and/or patients with a favourable baseline laboratory parameter profile can be treated, because they may benefit from therapy, but they must be carefully monitored. **Recently, interferon-free regimens combining sofosbuvir, a nucleotide polymerase inhibitor + daclatasvir (NS5a inhibitor) ± RBV (32) or sofosbuvir + simeprevir, a second-wave protease inhibitor ± RBV (33) have yielded very promising results in genotype 1 naive or null responders without cirrhosis. These IFN-free regimens need to be evaluated in cirrhotic patients. Some patients from the CUPIC cohort who failed to respond to interferon-based triple therapy are currently being retreated with sofosbuvir + ledipasvir (NS5a inhibitor) ± ribavirin in a prospective randomized trial (NCT01965535).**

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Figure legends

Figure 1A: Virological response with TVR according to the prior response to IFN/RBV therapy (ITT).

Figure 1B: SVR12 with TVR according to the HCV subtype and prior response to IFN/RBV therapy (ITT)

Figure 1C: SVR12 with TVR according to rapid virological response and the prior response to IFN/RBV therapy (ITT)

Figure 2A: Virological response with BOC according to the prior response to IFN/RBV therapy (ITT)

Figure 2B: SVR12 with BOC according to the HCV subtype and prior response to IFN/RBV therapy (ITT)

Figure 2C: SVR12 with BOC according to rapid virological response and the prior response to IFN/RBV therapy (ITT)

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Table 1: Baseline demographics and disease characteristics

Characteristics	**TVR (n = 299)**	**BOC (n = 212)**
Mean age (range), years	57.1 (27-83)	56.8 (34-81)
Male gender, n (%)	202 (67.6)	144 (67.9)
Mean body mass index (standard deviation) kg/m^2	26.5 (4.2)	26.3 (4.3)
Diabetes, n (%)	33 (11.0)	18 (8.5)
History of ascites or variceal bleeding, n (%)	5 (1.7)	6 (2.8)
Treatment history, n (%)		
- Prior relapse	117 (39.1)	92 (43.4)
- Prior partial response	135 (45.1)	94 (44.3)
- Prior null response	31 (10.4)	10 (4.7)
- Breakthrough	7 (2.3)	10 (4.7)
- Undetermined	9 (3.0)	6 (2.8)
Mean haemoglobin level (range), g/dL	14.5 (9.0-19.7)	14.8 (9.1-18.4)
Mean neutrophil count (range), $10^9/mm^3$	3.3 (0.8-8.5)	3.2 (0.5-8.5)
Mean platelet count (range), $/mm^3$	151,000 (18,000-604,000)	144,000 (33,900-346,000)
Mean alanine aminotransferase (range), IU/L	101 (0.2 – 456)	108 (5.0 - 474)
Mean prothrombin time ratio (range), (%)	86.5 (27-100)	87.1 (23-100)
Mean total bilirubin (range), µmol/L	15.4 (4.0-73.5)	15.1 (3.4-78.0)
Mean serum albumin (range), g/dL	40.0 (20.7-53.2)	40.4 (27.0-50.3)
Child-Pugh score, n (%)		
- A	285 (95.3)	198 (93.4)
- B	6 (2.0)	2 (0.9)
- C	0	0

- Undetermined	8 (2.7%)	12 (5.7)
Mean MELD score* (standard deviation)	8.1 (2.8)	8.1 (3.0)
- < 10, n (%)	225 (81.5)	153 (83.2)
- 10 - <13, n (%)	34 (12.3)	21 (11.4)
- ≥ 13, n (%)	17 (6.1)	10 (5.4)
Upper gastrointestinal endoscopy done, n (%)	149 (49.8)	109 (51.4)
Oesophageal varices, n (%)	54 (36.2)	41 (37.6)
REALIZE/RESPOND-2 exclusion criteria, n (%)	101(33.8)/140(46.8)	63(29.7)/87(41.0)
HCV genotype 1 subtype, n (%)		
- 1a	102 (34.1)	87 (41.0)
- 1b	166 (55.5)	104 (49.1)
- Others	31 (10.4)	21 (9.9)
HCV RNA ≥ 800,000 IU/mL, n (%)**	185 (62.0)	135 (65.2)
Creatinine clearance estimated using the Cockcroft-Gault formula, n (%)*		
<60 mL/min	**12 (4.2)**	**5 (2.7)**
60-90 mL/min	**70 (24.4)**	**48 (25.7)**
90 mL/min	**204 (71.4)**	**134 (71.6)**

* available in 276 patients for TVR and 184 patients for BOC

** available in 298 patients for TVR and 207 patients for BOC

*** **available in 286 patients for TVR and 187 patients for BOC**

Table 2: Baseline factors related to SVR12. Univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
	Odds ratio	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Prior treatment response						
Partial response	1			1		
Null response	0.265	0.107-0.655	0.0040	0.283	0.110-0.725	0.0086
Relapse or breakthrough	2.874	1.964-4.206	<0.0001	2.956	1.967-4.442	<0.0001
No lead-in phase	1.701	1.198-2.414	0.0030	1.784	1.198-2.657	0.0044
TVR	1.431	1.004-2.039	0.0472			
Platelet count >100,000/mm^3	2.207	1.437-3.389	0.0003	2.148	1.339-3.448	0.0015
Serum albumin ≥35g/L	2.718	1.543-4.791	0.0005			
No REALIZE exclusion criteria	1.661	1.139-2.422	0.0084			
No RESPOND-2 exclusion criteria	1.981	1.389-2.825	0.0002			
HCV subtype						
1a	1					
1b	2.713	1.844-3.993	<0.0001	2.499	1.624-3.846	<0.0001
Others	1.808	0.971-3.368	0.0619			

Gender, age, body weight, body mass index, diabetes, alcohol intake, cannabis smoking, haemoglobin, creatinine, alanine aminotransferase, HCV RNA, total bilirubin, prothrombin time, Child-Pugh score (A *vs* B), MELD score, and presence of oesophageal varices were tested in univariate analysis and were not significant

Table 3: Safety profile of the triple therapy including TVR (n = 299)

Events	Week 16	Week 60
Patients with serious adverse event, n (%)	137 (45.8)*	161 (53.8)**
Premature treatment discontinuation (any reason), n (%)	61 (20.4)	**144 (48.2)**
Premature treatment discontinuation due to SAEs, n (%)	44 (14.7)	**88 (29.4)**
Discontinuation of TVR alone	3 (1.0)	3 (1.0)
Discontinuation of RBV alone	1 (0.3)	3 (1.0)
RBV dose reduction	**22 (7.3)**	44 (14.7)
Peg-IFN dose reduction	**9 (3)**	17 (8.4)
Death, n (%)	5 (1.7)	8 (2.7)
Grade 3/4 infection, n (%)	20 (6.7)	29 (9.7)
Grade 3/4 hepatic decompensation, n (%)	6 (2.0)	14 (4.7)
Grade 3/4 asthenia, n (%)	16 (5.4)	19 (6.3)
Grade 3 rash / severe cutaneous adverse reaction, n (%)	14 (4.7) / 0	16 (5.3) / 0
Renal failure (creatinine clearance <50 mL/min), n (%)	5 (1.7)	6 (2.0)
Anaemia, n (%)		
Grade 2: 8.0 to ≤ 9.0 g/dL	57 (19.1)	65 (21.7)
Grade 3/4: < 8.0 g/dL	35 (11.7)	38 (12.7)
Erythropoietin use	158 (52.8)	169 (56.5)
Blood transfusion	47 (15.7)	53 (17.7)
Neutropenia, n (%)		
Grade 3: 500 to < 750 /mm^3	6 (2.0)	8 (2.7)
Grade 4: < 500/mm^3	3 (1.0)	5 (1.7)
Granulocyte-stimulating agent use	1 (0.3)	2 (0.7)

Thrombocytopenia, n (%)		
Grade 3: 20,000 to < 50,000/mm^3	31 (10.4)	35 (11.7)
Grade 4: < 20,000/mm^3	10 (3.3)	11 (3.7)
Thrombopoietin use	1 (0.3)	1 (0.3)

*356 SAEs in 137 patients, **537 SAEs in 161 patients

Table 4: Safety profile of the triple therapy including BOC (n = 212)

Events	Week 16	Week 60
Patients with serious adverse event, n (%)	64 (30.2)*	94 (44.3)**
Premature treatment discontinuation (any reason), n (%)	33 (15.6)	**99 (45.7)**
Premature treatment discontinuation due to SAEs, n (%)	10 (4.7)	**36 (17)**
Discontinuation of BOC alone	0 (0)	2 (0.9)
Discontinuation of RBV alone	0 (0)	3 (1.4)
RBV dose reduction	**11 (5.2)**	27 (12.7)
Peg-IFN dose reduction	**3 (1.4)**	14 (6.6)
Death, n (%)	1 (0.5)	3 (1.4)
Grade 3/4 infection, n (%)	4 (1.9)	8 (3.8)
Grade 3/4 hepatic decompensation, n (%)	6 (2.8)	9 (4.2)
Grade 3/4 asthenia, n (%)	10 (4.7)	13 (6.1)
Grade 3 rash / severe cutaneous adverse reaction, n (%)	0 / 0	2 / 0 (0.9)
Renal failure (creatinine clearance <50 mL/min), n (%)	0	1 (0.5)
Anaemia, n (%)		
Grade 2: 8·0 to ≤ 9.0 g/dL	50 (23.6)	52 (24.5)
Grade 3/4: < 8.0 g/dL	10 (4.7)	19 (9.0)
Erythropoietin use	93 (43.9)	119 (56.1)
Blood transfusion	14 (6.6)	25 (11.8)
Neutropenia, n (%)		
Grade 3: 500 to < 750 /mm^3	3 (1.4)	6 (2.8)
Grade 4: < 500/mm^3	6 (2.8)	7 (3.3)
Granulocyte-stimulating agent use	4 (1.9)	6 (2.8)

Thrombocytopenia, n (%)		
Grade 3: 20,000 to < 50,000/mm^3	10 (4.7)	15 (7.1)
Grade 4: < 20,000/mm^3	3 (1.4)	5 (2.4)
Thrombopoietin use	1 (0.5)	2 (0.9)

*153 SAEs in 64 patients, **313 SAEs in 94 patients

Table 5: Risk of death or severe complications and SVR12 according to serum albumin level and platelet count*

Factors	**Platelet count >100,000 /mm^3**	**Platelet count ≤100,000 /mm^3**
Serum albumin ≥35 g/L		
Patients, n (%)	306 (68.3%)	74 (16.5%)
Patients with severe complications or death, n (%)	19 (6.2%)	9 (12.2%)
Patients with SVR12, n (%)	168 (54.9%)	27 (36.5%)
Serum albumin <35 g/L		
Patients, n (%)	31 (6.9%)	37 (8.3%)
Patients with severe complications or death, n (%)	5 (16.1%)	19 (51.4%)
Patients with SVR12, n (%)	9 (29.0%)	10 (27.0%)

*Baseline albumin and platelet count were available in 448 patients (missing data in 63 patients for albumin and/or platelet count). 10 deaths were reported and analyzed in these 448 patients.