Observational Study

Boceprevir or telaprevir in hepatitis C virus chronic infection: The Italian real life experience

CLEO Study Group; Antonio Ascione, Luigi Elio Adinolfi, Pietro Amoroso, Angelo Andriulli, Orlando Armignacco, Tiziana Ascione, Sergio Babudieri, Giorgio Barbarini, Michele Brogna, Francesco Cesario, Vincenzo Citro, Ernesto Claar, Raffaele Cozzolongo, Giuseppe D’Adamo, Emilio D’Amico, Pellegrino Dattolo, Massimo De Luca, Vincenzo De Maria, Massimo De Siena, Giuseppe De Vita, Antonio Di Giacomo, Rosanna De Marco, Giorgio De Stefano, Giulio De Stefano, Sebastiano Di Salvo, Raffaele Di Sarno, Nunzia Farella, Laura Felicioni, Basilio Fimiani, Luca Fontanella, Giuseppe Foti, Caterina Furlan, Francesca Giancotti, Giancarlo Giolitto, Tiziana Gravina, Barbara Guerrera, Roberto Gulminetti, Angelo Iacobellis, Michele Imparato, Angelo Iodice, Vincenzo Iovinella, Antonio Izzi, Alfonso Liberti, Pietro Leo, Gennaro Lettieri, Ileana Luppino, Aldo Marrone, Ettore Mazzoni, Vincenzo Messina, Roberto Monarca, Vincenzo Narciso, Lorenzo Nosotti, Adriano Maria Pellicelli, Alessandro Perrella, Guido Piai, Antonio Picardi, Paola Pierri, Grazia Pietromaterra, Francesco Resta, Luca Rinaldi, Mario Romano, Angelo Rossini, Maurizio Russello, Grazia Russo, Rodolfo Sacco, Vincenzo Sangiovanni, Antonio Schiano, Antonio Sciambrà, Gaetano Scifo, Filomena Simeone, Annarita Sullo, Pierluigi Tarquini, Paolo Tundo, Alfredo Vallone

Antonio Ascione, Luca Fontanella, Michele Imparato, Department of Medicine, Center for Liver Diseases, “Buon Consiglio” - Fatebenefratelli Hospital, 80126 Naples, Italy
Luigi Elio Adinolfi, Barbara Guerrera, Internal Medicine Unit, Second University of Naples, 80125 Marcianise, Italy
Pietro Amoroso, Gennaro Lettieri, Paola Pierri, VI Division of Infectious Diseases, Cotugno Hospital, AORN “Ospedali dei Colli”, 80135 Naples, Italy
Angelo Andriulli, Angelo Iacobellis, Division of Gastroenterology, Casa Sollievo Sofferenza Hospital, IRCCS, 70131 San Giovanni Rotondo, Italy
Orlando Armignacco, Division of Infectious Diseases, Belcolle Hospital, 01100 Viterbo, Italy
Tiziana Ascione, Giorgio De Stefano, Nunzia Farella, IX Division of Infectious Diseases, Cotugno Hospital, AORN “Ospedali dei Colli”, 80135 Naples, Italy
Sergio Babudieri, Clinical of Infectious Disease, University of Sassari, 07100 Sassari, Italy
Giorgio Barbarini, Roberto Gulminetti, Infectious Disease IRCCS San Matteo, 27100 Pavia, Italy

Michele Brogna, Alfredo Vallone, Division of Infectious Diseases and Liver Unit, “G. Iazzolino” Hospital, 89900 Vibo Valentia, Italy
Francesco Cesario, Division of Infectious Diseases, “Anzianziata” Hospital, 87100 Cosenza, Italy
Vincenzo Citro, Giuseppe D’Adamo, Basilio Fimiani, Department of Internal Medicine, Umberto I Hospital, 84014 Nocera Inferiore, Italy
Ernesto Claar, Antonio Sciambrà, Internal Medicine, Ospedale Evangelico Villa Betania, 80147 Naples, Italy
Raffaele Cozzolongo, Division of Gastroenterology, IRCCS “S. de Bellis” Hospital, 70013 Castellana Grotte, Italy
Emilio D’Amico, Laura Felicioni, Internal Medicine Unit, Pescara-Penne Hospital, 65121 Pescara, Italy
Pellegrino Dattolo, Gastroenterology Unit, Marianise Hospital, 81025 Marcianise, Italy
Massimo De Luca, Liver Unit, AORN Cardarelli, 80131 Napoli, Italy
Vincenzo De Maria, Massimo De Siena, Sebastiano Di Salvo,
Ascione A et al. Boceprevir or telaprevir in HCV infection

Francesca Giancotti, Tiziana Gravina, Liver Unit, Policlinico “Mater Domini”, 80020 Catanzaro, Italy

Giuseppe De Vita, Service of Medical Day Hospital, “Rummo” Hospital, 82100 Benevento, Italy

Antonio Di Giacomo, Internal Medicine, Regina Margherita Hospital, 97013 Comiso, Ragusa, Italy

Rosanna De Marco, Pietro Leo, Ileana Luppino, Division of Gastroenterology, “Annunziata” Hospital, 87100 Cosenza, Italy

Giulio De Stefano, Grazia Pietromatera, Infectious Disease, Matera Hospital, 75100 Matera, Italy

Raffaele Di Sarno, Antonio IZZI, First Division of Infectious Diseases, Cotugno Hospital, AORN “Ospedali dei Colli”, 80135 Naples, Italy

Giuseppe Foti, Division of Infectious Diseases, AO Melacri­Bianchi-Morelli, 89121 Reggio Calabria, Italy

Caterina Furlan, Infectious and Tropical Disease, Policlinico Umberto I, 00185 Rome, Italy

Giancarlo Giotto, Grazia Russo, Division of Infectious Disease, Maria SS Addolorata Hospital, 84025 Eboli, Salerno, Italy

Angelo Iodice, Vincenzo Messina, Filomena Simeone, Division of Infectious Diseases, S. Anna and S. Sebastiano Hospital, 81100 Naples, Italy

Vincenzo Iovinella, Outpatients Service for Liver Diseases, “Loreto Crispi” Hospital, 80121 Naples, Italy

Alfonso Liberti, V Division of Infectious Diseases, Cotugno Hospital, AORN “Ospedali dei Colli”, 80135 Naples, Italy

Aldo Marrone, Luca Rinaldi, Department of Medical Surgical, Neurological, Geriatric, and Metabolic Sciences, Second University of Naples, Italy

Ettore Mazzoni, Liver Unit, Policlinico Casilino, 80132 Roma, Italy

Roberto Monarca, Medicine and Health Unit for Prisoners, Belcolle Hospital, 01100 Viterbo, Italy

Vincenzo Narciso, Internal Medicine Unit, “Ascaslesi” Hospital, 80100 Naples, Italy

Lorenzo Nosotti, Gastrointestinal and Liver Department, National Institute for Health, Migration and Poverty, 80199 Rome, Italy

Adriano Maria Pellicelli, Liver Unit, Azienda Ospedaliera San Camillo Forlanini, 00151 Rome, Italy

Alessandro Perrella, VII Division of Infectious Diseases, Cotugno Hospital, AORN “Ospedali dei Colli”, 80135 Naples, Italy

Guido Piai, Division of Gastroenterology, S. Anna and S. Sebastiano Hospital, 8100 Caserta, Italy

Antonio Picardi, Liver Unit, University “Campus Biomedico”, 80199 Rome, Italy

Francesco Resta, Division of Infectious Disease, Taranto Hospital, 74121 Taranto, Italy

Mario Romano, Liver Unit, “Sandro Pertini” Hospital, 80132 Rome, Italy

Angelo Rossini, Liver Unit, Service “Spedali Civili” Hospital, 24121 Brescia, Italy

Maurizio Russello, Liver Unit, Garibaldi-Nesima Hospital, 95121 Catania, Italy

Rodolfo Sacco, Gastroenterology and Metabolism Diseases Unit, AO Pisana, 56121 Pisa, Italy

Vincenzo Sangiovanni, III Division of Infectious Diseases, Cotugno Hospital, AORN “Ospedali dei Colli”, 80135 Naples, Italy

Antonio Schiano, Hepatology Unit, S. Giovanni di Dio Hospital, 80027 Frattamaggiore, Italy

Gaetano Scifo, Infectious Diseases Unit, P.O. Umberto I, 96100 Siracusa, Italy

Annarita Sullo, Infectious Diseases Unit, “Umberto 1st” Hospital, 84014 Nocera Inferiore, Italy

Pierluigi Tarquini, Infectious Diseases Unit, Giuseppe Mazzini Hospital, 64100 Teramo, Italy

Paolo Tundo, Division of Infectious Diseases, S. Caterina Novella Hospital, 75013 Catania, Italy

Author contributions: All authors of CLEO study group equally contributed to conception and design of the study, acquisition of data, review the draft, and approved the final version.

Institutional review board statement: The study was reviewed and approved by the CLEO Governing Board.

Informed consent statement: All study participants, or their legal representative, provided verbal informed consent prior to study enrolment as decided by the CLEO Governing Board and according to the local rules.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest regarding this study.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Antonio Ascione, MD, Consultant Hepatologist, Department of Medicine, Center for Liver Diseases, “Buon Consiglio” - Fatebenefratelli Hospital, Via A. Manzoni 220, 80126 Naples, Italy. antonio.ascione@pagenemediche.it
Abstract

AIM: To check the safety and efficacy of boceprevir/telaprevir with peginterferon/ribavirin for hepatitis C virus (HCV) genotype 1 in the real-world settings.

METHODS: This study was a non-randomized, observational, prospective, multicenter. This study involved 47 centers in Italy. A database was prepared for the homogenous collection of the data, was used by all of the centers for data collection, and was updated continuously. All of the patients enrolled in this study were older than 18 years of age and were diagnosed with chronic infection due to HCV genotype 1. The HCV RNA testing was performed using COBAS-TaqMan2.0 (Roche, LLQ 25 IU/mL).

RESULTS: All consecutively treated patients were included. Forty-seven centers enrolled 834 patients as follows: Male 64%; median age 57 (range 18-78), of whom 18.3% were over 65; mean body mass index 25.6 (range 16-39); genotype 1b (79.4%); diagnosis of cirrhosis (38.2%); and fibrosis F3/4 (71.2%). The following drugs were used: Telaprevir (66.2%) and PEG-IFN-alpha2a (67.6%). Patients were naïve (24.4%), relapers (30.5%), partial responders (14.8%) and null responders (30.3%). Overall, adverse events (AEs) occurred in 617 patients (73.9%) during the treatment. Anemia was the most frequent AE (52.9% of cases), especially in cirrhotic. The therapy was stopped for 14.6% of the patients because of adverse events or virological failure (15%). Sustained virological response was achieved in 62.7% of the cases, but was 43.8% in cirrhotic patients over 65 years of age.

CONCLUSION: In everyday practice, triple therapy is safe but has moderate efficacy, especially for patients over 65 years of age, with advanced fibrosis, non-responders to peginterferon + ribavirin.

Key words: Boceprevir; Telaprevir; Chronic hepatitis; Antiviral therapy; Peg-interferon; Ribavirin

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This study describes the role of antiviral therapy for chronic hepatitis C virus infections in everyday practice. Boceprevir or telaprevir, in combination with pegylated interferon and ribavirin, were used in this multicenter study organized by the Italian Association of Hospital Hepatologists (CLEO). A total of 834 patients were enrolled with this first available combination of direct-acting antiviral drugs. The data on the efficacies were quite similar to those produced by the registration studies; however, in the real world experience, patients were older and had more advanced liver disease. In this category of patients, the sustained virological response was less than 50%.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is one of the main causes of liver cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) and liver transplantation worldwide. Pegylated interferon-alpha (P) and ribavirin (R) have been the backbone of HCV treatment for more than a decade. In 2011, the approval of telaprevir (TVR) and boceprevir (BOC), two protease inhibitors (PI), opened the first generation of direct antiviral agents (DAAs) for the treatment of genotype 1 HCV infection.

In many randomized studies, triple therapy (the combination of P plus R with PI, such as TVR or BOC) is demonstrated to be more effective than P plus R alone, with an increased likelihood of sustained virological response (SVR) of more than 30%, when compared with the dual therapy (P + R), reaching 68%-75% of naive patients and 29%-83% of the experienced patients depending on the previous response to P + R[1-4]. The increase in SVR is associated with more side effects, and some of them, such as anemia and rash, were frequently causes of the withdrawal from treatment. However, as is well known, in the registered trials, the number of difficult-to-treat patients is rather small (cirrhotic, elderly, null responders to previous treatments and patients with comorbidities). However, even with restricted criteria for enrollment in phase 3 studies, a number of patients had
to stop the triple therapy due to either viral failure or adverse events (12%-15%).

TVR/BOC, approved for reimbursement in Italy in December 2012, have been used since January 2013. Since then, the group of the Association of Hospital Hepatologists (CLEO DAAs Study Group) was deeply involved in using these drugs, and the Governing Board of the Association decided to collect data from the Hospital centers belonging to the CLEO. The aim of our study was to determine what happens in everyday practice in terms of safety and efficacy using the triple therapy.

**MATERIALS AND METHODS**

**Study design**

This study was a non-randomized, observational, prospective, multicenter. This study involved 47 centers in Italy. A database was prepared for the homogenous collection of the data, was used by all of the centers for data collection, and was updated continuously.

**Subjects**

All of the patients enrolled in this study were older than 18 years of age, were diagnosed with chronic infection due to HCV genotype 1, and were consecutively seen in at least one of the centers between January 2013 and June 2014. No distinction was made between naive and previously treated patients. With regard to age, patients were divided into the following three groups: (1) less than 50; (2) between 50 and 65; and (3) over the age of 65. In this manner, we tried to avoid the division into only two categories (under 65 and over 65), which is presented in many papers and flattens the differences. Hepatitis B virus/human immunodeficiency virus positive patients or patients suffering from chronic liver disease due to other etiologies were excluded.

**Treatment**

Each center made the choice between TVR or BOC and Peg-IFN-alpha2a or Peg-IFN-alpha2b; patients were also treated with ribavirin (dose depending on the type of P chosen). The drugs were administered according to the manufacturer's instructions. TVR was administered with P + R for 12 wk followed by 36 wk of P + R; while patients treated with BOC received 4 wk of P + R (lead-in phase) followed by 44 wk of BOC + P + R. Patients treated with BOC or TVR had to respect the stopping rule concerning the kinetics of the viral load as follows: BOC patients with an HCV-RNA at week 12 greater than or equal to 100 IU/mL or detectable at 24 wk had to stop the therapy, while TVR patients with an HCV-RNA greater than 1000 IU/mL at week 4 or 12 or detectable at week 24 had to stop the treatment. They were classified as non-responders because of the virological failure.

**Methods**

Fibrosis was evaluated by a liver biopsy or by measuring the liver stiffness according to the manufacturer’s instructions (Fibroscan®, Echosens, Paris, France). The results were expressed in kilopascal (kPa), and the cut-off values according to the literature were as follows: F1 was defined by a liver stiffness < 7.0 kPa; F2 was defined by a liver stiffness between 7.1-9.5; F3 was defined by a liver stiffness between 9.6-12.4; F4 (cirrhotic patients) was defined by liver stiffness values of up to 12.5 kPa[5].

Patients, according to their response to the previous treatment, were categorized as naive (never treated with antiviral drugs); relapers (patients who were HCV RNA negative at the end of treatment and HCV RNA positive during the follow-up); partial responders (those with a reduction of HCV RNA during the treatment, but never become HCV RNA negative); and null responders (patients without any change in HCV RNA during the treatment and thereafter)[9].

AEs were graded by the investigators, according to the NIH grading system (CTCAE version 4.0). Hematological disorders, mainly anemia, were managed by reducing the ribavirin dose, giving erythropoietin, and/or with a blood transfusion, at the discretion of the physicians of each center. Hepatic decompensation during the therapy was defined by the new onset of one of the following clinical manifestations: Ascites, variceal hemorrhage, hepatic encephalopathy and onset of HCC.

A quantification of the HCV-RNA level was performed at baseline, 4 wk, 8 wk, 12 wk, the end of treatment, and 12 wk after the end of treatment. The HCV-RNA level was detected using real-time polymerase chain reaction (COBAS® TaqMan® HCV Test v2.0, Roche Diagnostics, Basel, Switzerland) with a lower limit of detection of 25 IU/mL. SVR was defined as HCV-RNA below the level of quantification 12 wk after the end of treatment.

**Statistical analysis**

All consecutively treated patients were included; data were analyzed according to the intention-to-treat principle. A preliminary descriptive analysis of the main demographic, virological and clinical baseline variables [gender, age, body mass index (BMI), HCV genotype, HCV RNA level, fibrosis grade, IL-28B, type of response to previous antiviral therapy, biochemical laboratory tests, concomitant diseases, side effects, and virological response during, at the end, and 12 wk after the end of therapy] of the entire population under investigation was carried out. Statistics measurements were as follows: Mean and standard deviation, mean standard error and 95%CI, median and range (when appropriate). At a later stage, univariate analysis and one-way ANOVA were conducted to verify the relationships between each independent variable and the dependent variable (SVR12). A $\chi^2$ test for categorical variables and a t-test or Mann-Whitney test (when appropriate) for quantitative variables was used. A two-tailed $P$-value $< 0.05$ was considered to indicate statistical significance. Then, we looked for multicollinearity between those independent variables that statistically associated with SVR12. Finally, a multivariable logistic-regression analysis (step-
Eight hundred and thirty-four Caucasian patients observed in the 47 participating centers from January 2013 to June 2014 were enrolled, of whom 12.1% were also alcohol abusers, and 11.5% were affected by type 2 diabetes.

The two treatments (BOC/TVR) were analyzed together. The characteristics of the patients are reported in Table 1.

The majority of our patients were affected by genotype 1b (79.4%) and cirrhosis (38.2%). Among these 319 cirrhotic patients, 70.8% had a Child-Turcotte-Pugh Score of A5, 23.1% had A6; while 4.5% were B7 and 1.6% were B8. According to the response to previous treatments, 24.4% were naive, 30.5% were relapers, 14.8% were partial responders and 30.3% were null-responders. According to the fibrosis grade, 7.7% of patients were F1, 21.1% were F2, 33.0% were F3 and 38.2% were F4.

HCV genotype 1b (79.4%) infections were more frequent than HCV 1a (19.2%), but the HCV genotype was not defined as 1b or 1a in 1.4% of the cases. As expected, in this population of relapers and non-responders to prior antiviral therapy, only 13.5% of the patients had an IL-28B genotype CC. However, not all of the centers had this test available, but it was carried out on 61.5% of treated patients. Each center decided the choice of therapy, with the following percentage: TVR 66.2%, BOC 33.8%, Peg-IFN alpha2a 67.6% and Peg-IFN alpha2b 32.4%.

Overall, 70.4% of the patients completed a full course of therapy, while the treatment was stopped due to virological failure in 15% of the cases and for adverse events in 14.6%.

The overall SVR rate was 62.7% (95%CI: 59.1-66.3), while 70.1% of the patients had undetectable HCV-RNA levels at the end of triple therapy with a rate of relapse of 7.3% (Table 2). According to age, SVR was observed in 67.4% of patients < 50 years, 63.1% of the patients whose ages ranged from 50 to 65, and 55.3% of patients > 65 years (P = 0.037). SVR was observed in 65.7% of the naive patients, 73.7% of relapers, 67.2% of partial responders and 55.1% of the null responders (P = 0.012). Only 53.4% of cirrhotic patients had an SVR vs the 72.7% of patients with fibrosis F1 (P = 0.003), 73.4% with F2 (P = 0.0001), and 63.3% with F3 (P = 0.013); the lower rate of SVR of 43.8% was observed in cirrhotic patients over 65 years of age (P = 0.0001). When we compared the SVR observed in the categories F0/1/2 and 3 (68.1%) vs F4 (53.4%), there was a statistically significant difference (P = 0.0001). As for the relationship between SVR and the IL28B, the CC (70%), CT (57.5%), and TT (45.7%) groups, there was a statistically significant difference (P = 0.029) in favor of the CC group. Alcohol did not affect the percentage of SVR, while type 2 diabetes was statistically associated with SVR (OR = 0.55; 95%CI: 0.34-0.87, P = 0.006). The univariate analysis showed that six factors were independently associated with SVR. These factors were as follows: (1) a relapse after P + R treatment; (2) the stage of fibrosis; (3) age; (4) gender; (5) diabetes; and (6) the IL-28B status; while BMI, HCV-RNA at baseline, biochemistry at baseline and genotype subtype were not associated with SVR. The multivariate analysis with logistical regression revealed that only fibrosis F0/F1/F2 stages, IL-28B-CC and the absence of diabetes are independently associated.

**RESULTS**

Eight hundred and thirty-four Caucasian patients observed in the 47 participating centers from January 2013 to June 2014 were enrolled, of whom 12.1% were also alcohol abusers, and 11.5% were affected by type 2 diabetes.

The two treatments (BOC/TVR) were analyzed together. The characteristics of the patients are reported in Table 1.
with SVR \((P < 0.05)\). The odds ratios for fibrosis stages F0/F1/F2 and F3 vs F4 (the reference category) were 2.3 (95%CI: 1.3-3.8; \(P = 0.002\)) and 1.5 (95%CI: 0.9-2.3; \(P = 0.096\)), respectively. The OR for IL28B-CC and IL28B-CT vs IL28B-TT (the reference category) were 3.2 (95%CI: 1.5-6.7; \(P = 0.003\)) and 1.5 (95%CI: 0.9-2.4; \(P = 0.11\)), respectively. As for diabetes, the odds ratio was 1.8 (95%CI: 0.9-3.5; \(P = 0.075\)).

### Safety

Overall, AEs occurred in 617 patients (73.9%) during the treatment (Table 3). A total of 122 (14.6%) of the patients suspended the therapy due to AEs. In general, females stopped the treatment more often than males (16% vs 11%; \(P = 0.043\)). With increasing age, there was a statistically significant increase in AEs (9.4% vs 12.6% vs 18.4%; \(P = 0.040\)). There was no statistically significant difference in relation to subtype \((1\# 13.7\% \text{ vs } 9.3\% \text{ vs } 1; \text{ } P = 0.18\); nor was there a statistically significant difference in relation to the histological diagnosis \((P = 0.58)\) even if the F4 class showed the highest percentage \((13.8\%)\) of AEs compared to the other classes as follows: F3 (12.9%), F2 (9.8%), F1 (11.7%) and F0 (0.6%, four patients only in this group).

Anemia was the most frequent AE \((52.9\%)\ of cases), especially in cirrhotic as already described\([9]\), followed by asthenia \((39.6\%)\), neutro-thrombocytopenia \((29.6\%)\), rash/itching \((23.2\%)\), dysgeusia \((8.6\%)\), psychiatric disorders \((6.7\%)\), anorectal discomfort \((5.9\%)\) and others \((14.9\%)\). Among this last group, we recorded the following: Gastrointestinal disorders \((23\%)\), pulmonary infections \((9\%)\), ascites \((3\%)\), pancreatitis \((2\%)\), thrombosis of retina \((2\%)\), and new onset of cancer as follows: Hepatocellular carcinoma \((1\%)\), breast \((1\%)\), and kidney \((1\%)\). Anemia was observed regardless of the DAA used, while rash was more frequently observed in the TVR treated patients. The main AEs that led to treatment discontinuation were rash \((29.8\%)\) and anemia \((23.4\%)\). There were no fatalities as the included patients had cirrhosis, but not as advanced as in the French study\([8]\) where the 2.2% of the patients died.

### DISCUSSION

This study, conducted in 47 hospital centers in Italy, enrolled 834 patients consecutively seen in clinical settings. Because there was no selection of the cases, all of the patients seen and judged to be treatable by each center were included. For this reason, we can safely assume that this study mirrors what happens in real life. This is the main reason of the need for studies that monitor the safety after registration of the authorization of the prescription of new drugs. It is at this stage that many older patients with morbidity, concurrently taking other medications, are enrolled. Observational studies, such as those already published and our own, serve not only to validate the results of pivotal trials but also to provide information on safety and predictors of response that helps to more appropriately use the new drugs. Some aspects should be underlined, such as the age of the patients \((18.3\% \text{ more than } 65\%)\, the percentage of advanced liver disease (Fibrosis score F3 plus F4 = 70.9%) and the high percentage \((75.6\%)\ of patients previously treated with P + R. It is quite remarkable that the percentage of patients with compensated cirrhosis was 37.1%; while in the registration studies, this group of difficult-to-treat patients did not exceed 15%.

When we analyzed the differences between the major registration studies conducted using TVR/BOC and our findings, the first observation was that the AEs causing discontinuation of drugs were different from those reported in the phase 3 trials, where these percentages ranged between 8%-15%. The true strength of “real life” studies is the inclusion of patients who visit the clinics in every day practice and represent HCV-related disease at every stage. The only weakness is that they are not

### Table 2 Percentage of sustained virological response according to demographics and clinical characteristics

<table>
<thead>
<tr>
<th>Feature</th>
<th>SVR (%)</th>
<th>RVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR 12*</td>
<td>62.7%</td>
<td>66.5%</td>
</tr>
<tr>
<td>HCV-RNA negative at EOT</td>
<td>70.1%</td>
<td></td>
</tr>
<tr>
<td>Relapsing</td>
<td>7.3%</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 50 yr</td>
<td>67.4%</td>
<td></td>
</tr>
<tr>
<td>50-65 yr</td>
<td>63.1%</td>
<td></td>
</tr>
<tr>
<td>&gt; 65 yr</td>
<td>55.3%</td>
<td></td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive</td>
<td>65.7%</td>
<td></td>
</tr>
<tr>
<td>Relapsing</td>
<td>73.7%</td>
<td></td>
</tr>
<tr>
<td>Partial responder</td>
<td>67.2%</td>
<td></td>
</tr>
<tr>
<td>Null responder</td>
<td>55.1%</td>
<td></td>
</tr>
<tr>
<td>Fibrosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>72.7%</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>73.4%</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td>63.3%</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>53.4%</td>
<td></td>
</tr>
<tr>
<td>F4 &gt; 65 yr</td>
<td>43.8%</td>
<td></td>
</tr>
</tbody>
</table>

\*HCV-RNA negative at week 4; \*Those who achieved EOT but had HCV-RNA positive at week 12; \*HCV-RNA negative 12 wk after the EOT.

### Table 3 Adverse events (%) and treatment discontinuation

<table>
<thead>
<tr>
<th>Adverse events (%) and treatment discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>Treatment discontinuation (122 cases; 14.6%)</td>
</tr>
<tr>
<td>Rash/Itch</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Asthenia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>Pancytopenia</td>
</tr>
<tr>
<td>Neutro/thrombocytopenia</td>
</tr>
<tr>
<td>Others (see text)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events (73.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Asthenia</td>
</tr>
<tr>
<td>Neutro/thrombocytopenia</td>
</tr>
<tr>
<td>Dysgeusia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>Anorectal symptoms</td>
</tr>
<tr>
<td>Others (see text)</td>
</tr>
</tbody>
</table>

1HCV-RNA negative at week 4; 2Those who achieved EOT but had HCV-RNA positive at week 12; 3HCV-RNA negative 12 wk after the EOT.
randomized, and specialized centers in different parts of the country are involved, which favors a certain degree of heterogeneity. However, this aspect is also present in the pivotal studies in which many centers participate, often scattered in different countries. Analyzing other studies similar to ours, the percentages of drug discontinuation varies from a minimum of 8% to a maximum of 38%[^10]. However, it is difficult to entirely blame DDAs for some AEs, as in addition to BOC and TVR, there were two drugs, including P and R, with AEs well known for many years, especially anemia, itching, and nervousness. In this study, among the AEs causing withdrawal from treatment, rash (29.5%) was the most frequent, although we did not observe DRESS syndrome or toxic epidermal necrolysis.

Rash was detected in both treatment groups, although it was more frequent in patients treated with TVR. Anemia was the second most important AE leading to discontinuation of therapy. In 11% of the patients, it was necessary to perform blood transfusions, while in 25%, epoetin was administered. Other cases were simply treated with a dose reduction of ribavirin. As for the AEs not causing withdrawal from therapy, we did not find remarkable differences with the pivotal trials (Table 3).

The SVR at 12 wk after the end of treatment was achieved by 62.7%, more than that achieved by the other similar studies. The high number of patients with cirrhosis and the presence of older patients explain the results, such as SVR, which was a percentage lower than that obtained from the pivotal studies. In naive patients, the results were similar to those previously obtained by partial responders, while those who had the best performance (SVR = 73.7%) were those who had a relapse at the end of the previous treatments. Similar data for this category of patients were achieved by the other studies[^10] for experienced patients. Null responder patients to previous treatments had an SVR of 55.1%, better than that reported in other similar studies, whereas in one study[^10], the SVR was less than 20%. The most relevant finding of this study was the negative correlation between the SVR and fibrosis grade. This result has been recently confirmed[^13]. In fact, as reported in Table 3, the worst result (SVR = 43.8%) was achieved in patients with cirrhosis, who were older than 65 years of age. Indeed, these categories of patients (elderly, with cirrhosis and with many failures to previous treatments) represent the majority of patients requiring treatment today. Multivariate analyses showed that the most important factors linked to SVR were the grade of fibrosis, IL-28B-CC and not being diabetic.

In conclusion, the treatment with first generation PI (BOC/TVR) plus P + R is quite safe, but its efficacy is limited, especially for elderly cirrhotic patients. This information is very useful as DDA IFN-free drugs may change the antiviral therapy options for HCV, and there is no doubt that in many countries, these drugs will only be selectively available due to cost. Therefore, real life studies on “old” less expensive DDAs could be very useful for establishing drug delivery policies in relation to the resources available in each country.

**ACKNOWLEDGMENTS**

The CLEO Study Group thanks Michele Imparato, MD, for the data management, Massimo De Luca, MD, for the statistical analysis and Antonio Ascione, MD, for writing the draft.

**REFERENCES**

Ascione A et al. Boceprevir or telaprevir in HCV infection


P- Reviewer: Abd El-Wahab EW, Li J, Lawless MW, Tang ZH
S- Editor: Gong XM L- Editor: A E- Editor: Li D