

## Observational Study

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

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**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.

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**Manuscript source:** Invited manuscript

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Received: February 23, 2016

Peer-review started: February 24, 2016

First decision: April 15, 2016

Revised: June 23, 2016

Accepted: July 20, 2016

Article in press: July 22, 2016

Published online: August 8, 2016

## 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%), relapsers (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

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**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%.

CLEO Study Group; Ascione A, Adinolfi LE, Amoroso P, Andriulli A, Armignacco O, Ascione T, Babudieri S, Barbarini G, Brogna M, Cesario F, Citro V, Claar E, Cozzolongo R, D'Adamo G, D'Amico E, Dattolo P, De Luca M, De Maria V, De Siena M, De Vita G, Di Giacomo A, De Marco R, De Stefano G, De Stefano G, Di Salvo S, Di Sarno R, Farella N, Felicioni L, Fimiani B, Fontanella L, Foti G, Furlan C, Giancotti F, Giolitto G, Gravina T, Guerrero B, Gulminetti R, Iacobellis A, Imperato M, Iodice A, Iovinella V, Izzi A, Liberti A, Leo P, Lettieri G, Luppino I, Marrone A, Mazzoni E, Messina V, Monarca R, Narciso V, Nosotti L, Pellicelli AM, Perrella A, Piai G, Picardi A, Pierri P, Pietromatera G, Resta F, Rinaldi L, Romano M, Rossini A, Russello M, Russo G, Sacco R, Sangiovanni V, Schiano A, Sciambra A, Scifo G, Simeone F, Sullo A, Tarquini P, Tundo P, Vallone A. Boceprevir or telaprevir in hepatitis C virus chronic infection: The Italian real life experience. *World J Hepatol* 2016; 8(22): 949-956 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i22/949.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i22.949>

## 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 naïve patients and 29%-83% of the experienced patients depending on the previous response to P + R<sup>[1-4]</sup>. 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 in-

structions (Fibroscan<sup>®</sup>, 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<sup>[5]</sup>. Patients, according to their response to the previous treatment, were categorized as naive (never treated with antiviral drugs); relapsers (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)<sup>[6]</sup>.

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<sup>®</sup> TaqMan<sup>®</sup> 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-



**Table 1** Baseline characteristics of 834 patients enrolled

Age	Median 57 (range 18-78); age > 65: 18.3%
Sex	Male 64%, female 36%
BMI	Mean 25.6 ( $\pm$ SD) = 3.2 (range 16-39)
Genotype (%)	
1a	19.2
1b	79.4
1	1.4
HCV-RNA	
HCV-RNA $\leq 10^6$	42%
HCV-RNA $> 10^6$	58%
IL 28B (%) <sup>1</sup>	
TT	21.1
CT	65.4
CC	13.5
Fibrosis (%)	
F1	7.7
F2	21.1
F3	33
F4	38.2
Cirrhosis (CTP%)	
A5	70.8
A6	23.1
B7	4.5
B8	1.6
Previous treatment (%)	
Naive	24.4
Relapser	30.5
Partial responder	14.8
Null responder	30.3
Comorbidity (%)	
Diabetes mellitus	11.5
Alcohol	12.1

<sup>1</sup>Available on 513 patients (61.5%). BMI: Body mass index; HCV: Hepatitis C virus; IL: Interleukin; CTP: Child-Turcotte-Pugh classification; SD: Standard deviation.

wise selection procedure) was conducted to assess the relationship between the SVR and the pre-specified demographic and baseline clinical characteristics.

We have not carried out a statistical analysis comparing the two treatments. The reasons are as follows: (1) as already mentioned, this comparison was not one of the purposes of the study; and (2) each center not only chose BOC or TVR in its absolute discretion but also the type of pegylated interferon. This aspect would determine the division into the four groups with a very different dimension and would not provide acceptable results. Moreover, other studies similar to ours did not make any comparative analysis between the two treatments because of the same reasons<sup>[7,8]</sup>.

All statistical analyses were performed using the software package SPSS for Windows (Rel SPSS 15.0; SPSS Chicago, IL, United States).

## 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 to-

gether. 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 relapsers, 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 relapsers 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 relapsers, 67.2% of partial responders and 55.1% of the null responders ( $P = 0.012$ ). Only 53.4% of the 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

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

RVR <sup>1</sup>	66.5%
HCV-RNA negative at EOT	70.1%
Relapse <sup>2</sup>	7.3%
SVR 12 <sup>3</sup>	62.7%
Age	
< 50 yr	67.4%
50-65 yr	63.1%
> 65 yr	55.3%
Previous treatment	
Naive	65.7%
Relapser	73.7%
Partial responder	67.2%
Null responder	55.1%
Fibrosis (%)	
F1	72.7%
F2	73.4%
F3	63.3%
F4	53.4%
F4 > 65 yr	43.8%

<sup>1</sup>HCV-RNA negative at week 4; <sup>2</sup>Those who achieved EOT but had HCV-RNA positive at week 12; <sup>3</sup>HCV-RNA negative 12 wk after the EOT. RVR: Rapid virological response; EOT: End of treatment; SVR: Sustained virological response; HCV: Hepatitis C virus.

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 IL-28B-CT vs IL-28B-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 (1b 13.7% vs 9.3% 1a;  $P = 0.18$ ); 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<sup>[9]</sup>, 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 cases), pulmonary infections (9), ascites (3), pancreatitis (2), thrombosis of retina (2), and new onset of cancer as follows: Hepatocellular carcinoma (1), breast (1), and

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

Adverse events (73.9%)	
Anemia	52.9
Asthenia	39.6
Neutro/thrombopenia	29.6
Dysgeusia	8.6
Psychiatric disorders	6.7
Anorectal symptoms	5.9
Others (see text)	14.9
Treatment discontinuation (122 cases; 14.6%)	Number of cases
Rash/Itch	36 (29.5%)
Anemia	28 (22.9%)
Asthenia	18 (14.7%)
Psychiatric disorders	6 (5%)
Pancytopenia	3 (2.5%)
Neutro/thrombopenia	3 (2.5%)
Others (see text)	28 (22.9%)

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<sup>[8]</sup> 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% 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

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%<sup>[7-10]</sup>. 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<sup>[9,11,12]</sup> 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<sup>[10]</sup>, 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<sup>[13]</sup>. 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.

## COMMENTS

### Background

Protease inhibitors (boceprevir or telaprevir) in combination with pegylated interferons and ribavirin are the first direct antiviral therapy for chronic infections with hepatitis C virus (HCV) genotype 1. They were introduced in 2011 and since then have been a step forward in the development of this therapy. In Italy, these therapies were introduced in 2013 and the Italian Association of Hospital hepatologists (CLEO) has begun, among the members of the association, the data collection.

### Research frontiers

This study represents one of the few real-life studies with high number of cases, published in the international field and the only one regarding the Italian patients. Compared to the registration studies, the collection of data from patients who are treated every day provides valuable data to validate in clinical practice this treatment.

### Innovations and breakthroughs

Therefore, the present study tested in practice the first two innovative drugs in chronic infections with HCV therapy that were expected at least for ten years. With their arrival in the therapeutic baggage of hepatologists, the authors have obtained results certainly better than the performance of conventional therapy with interferon and ribavirin alone, which has represented the standard of care for about fifteen years.

### Applications

The data generated from this study show that these drugs have an acceptable safety profile but their effectiveness, especially in cirrhotic patients and with over 65 years of age, is quite modest. Their greater efficacy is obtained in patients with non-advanced liver damage. The new drugs, which are currently on the market for hepatitis C, are more active than the triple therapy, but their cost is extremely high. Therefore, these studies are of great social importance because, in countries that do not have an economy that allows the purchase of these drugs, the triple therapy can be offered with excellent results, choosing carefully the categories of patients to be treated.

### Terminology

The letter "F" expresses the degree of fibrosis in the liver. In this study this aspect was defined by liver biopsy or by the Fibroscan tool, which, in a non-invasive way, is able to define the degree of rigidity and, therefore, the actual degree of fibrosis in the liver. The physical principle is that the higher the number in kilopascals, the higher the degree of fibrosis.

### Peer-review

This topic of study is very topical and important. The authors' concept and ideas for this investigation is very note worthwhile and studies of real life experiences are most useful for the field.

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**P- Reviewer:** Abd El-Wahab EW, Li J, Lawless MW, Tang ZH

**S- Editor:** Gong XM **L- Editor:** A **E- Editor:** Li D







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