

Boceprevir for chronic HCV genotype 1 infection in treatment-experienced patients with severe fibrosis or cirrhosis: The Greek real-life experience

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Abstract

Background The aim of our study was to evaluate the safety and efficacy of triple therapy using boceprevir (BOC) with pegylated interferon (pIFN)/ribavirin (RBV) in chronic hepatitis C (CHC) genotype 1 (G1) treatment-experienced patients with advanced fibrosis or compensated cirrhosis.

Methods We report the Greek experience on the first CHC patients who received BOC-based regimen. From September 2011 to June 2012, 26 treatment-experienced CHC patients and G1 with bridging fibrosis or compensated cirrhosis received 48 weeks of BOC+pIFN+RBV antiviral therapy. Data on complete blood counts and HCV RNA levels were obtained prior to therapy, at treatment weeks 4, 8, 12, 24, 36, 48 and 24 weeks after the end of treatment.

Results A full set analysis was performed in 25 of 26 patients. Nine patients (36%) achieved sustained viral response (SVR). Ten patients (40%) stopped the therapy because of futility rules and 3 (12%) due to adverse events. Four patients (16%) developed a virological breakthrough (3 of those presented futility rules as well) and 2 (8%) relapse. All patients who achieved SVR had G 1b, 6 (67%) were non-cirrhotic and 5 (55%) had >1 log decline in baseline HCV RNA levels at week 4 of the treatment. There were no deaths, while two patients were hospitalized due to side effects.

Conclusion The triple therapy with BOC+pIFN+RBV in this cohort of real-life treatment-experienced CHC G1 patients and advanced liver disease was safe offering cure in the majority of those who could tolerate and complete treatment under a close monitoring.

Keywords Protease inhibitors, boceprevir, HCV G1 infection

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Introduction

Chronic hepatitis C (CHC) affects more than 170 million people worldwide and remains one of the main causes of cirrhosis, liver failure and hepatocellular carcinoma (HCC) [1]. For more than 10 years the standard of care (SOC) was the dual combination of pegylated interferon- α (pIFN) and ribavirin (RBV) achieving sustained viral response (SVR) in approximately 40% of the genotype (G) 1/4 and 70-80% of G 2/3 patients [2-5]. In 2011 pIFN containing regimens with 1st generation protease inhibitors were licensed for CHC G1 patients becoming the new SOC in many countries for CHC patients with G1 compensated liver disease. However, availability and use of triple based-therapy liver disease (boceprevir or telaprevir + pIFN + RBV) was mainly in wealthy European countries based on their healthcare system and not to the rest due to the significant increase in cost of therapy [6].

Boceprevir (BOC) in combination with pIFN+RBV [6] has been demonstrated to result in significantly higher SVR rates compared to dual treatment with pIFN+RBV (63-66% vs 38% for treatment-naïve patients and 59-66% vs 21% in treatment-experienced patients) [7,8]. The severity of liver disease and the history of previous no response have been significantly associated with lower response to antiviral treatment [9-19]. Despite the promising response rates, the use of triple therapy has remained rather limited because of the complexity of the regimen and a number of safety and cost issues.

In this study we investigated the safety, tolerability and efficacy of BOC in combination with pIFN+RBV in patients with CHC G1 and advanced disease who had no other available option following previous treatment failures with SOC.

Patients and methods

Patients

From September 2011 until June 2012, patients from 5 tertiary centers throughout Greece with CHC G1 and bridging fibrosis or compensated cirrhosis who had failed to achieve SVR under previous treatment were given BOC as part of a case-by-case named patient program (NPP). BOC was provided free by Merck Sharp & Dohme (MSD Greece).

Eligible patients were aged 18 years or older with confirmed CHC G1 infection and detectable serum hepatitis C virus (HCV) RNA concentrations. We established the presence of advanced fibrosis or cirrhosis by liver biopsy using the METAVIR score and/or by transient elastography (Fibroscan, Echosens Paris), where the cut off value for advanced fibrosis and cirrhosis was set at 9.5 kPa and 12.5 kPa, according to previous publications [20]. Patients with cirrhosis were eligible if an ultrasound within the previous six months showed no signs of HCC. All patients had well-compensated bone marrow with neutrophils $>1500/\text{mm}^3$, Hb $>12/13$ g/dL female/male and liver function with serum albumin over 3.5 g/dL.

Exclusion criteria included hepatic decompensation (as indicated by the presence of ascites, encephalopathy

or a history of variceal bleeding), non-G1 CHC infection, malignancy, organ transplantation, cardiac or renal failure and hematologic disorders, patients with co-infection (HIV or hepatitis B virus) and evidence of substance abuse involving alcohol or intravenous drugs and patients under medications whose pharmacokinetics can affect or can be affected by BOC. Serum HCV RNA levels were measured using the TaqMan 2.0 assay (Roche Diagnostics) with a lower limit of quantification and detection of <15 IU/mL, used for decision making as per summary of product characteristics of BOC label.

The Greek National Health Authorities as well as each hospital's Ethics Committee had provided approval of NPP. Written informed consent was obtained from all patients.

Treatment algorithms and follow up

All patients received therapy with pIFN alpha-2b or pIFN alpha-2a and RBV during the first 4 weeks (lead-in period). At treatment week 5, BOC was added. BOC (Victrelis, MSD) was administered orally at a dose of 800 mg t.i.d. in four capsules of 200 mg each with food taken together.

The treatment duration for non-cirrhotic patients was an initial period (lead in) with pIFN alfa + RBV, followed by triple therapy with BOC+ pIFN alfa + RBV for 32 weeks and then 12 weeks with the combination of pIFN alfa + RBV. Treatment duration for patients with cirrhosis or for patients with previous null response was 4 weeks of lead in with pIFN alfa + RBV followed by 44 weeks of triple therapy with BOC+pIFN+RBV.

Definitions of response and non-response

SVR was defined as undetectable HCV RNA (<15 IU/mL) at week 24 after the end of treatment. End of treatment response was defined as undetectable HCV RNA at the end of treatment. Null responders were defined as patients who previously failed in pIFN alfa + RBV treatment and who did not achieve $>2\text{-log}_{10}$ decline in HCV viral RNA levels at 12 weeks of therapy or had $<0.5\text{-log}_{10}$ HCV RNA decline in viral load at 4 weeks of therapy with pIFN alfa + RBV [6,8].

Partial responders were defined as patients who previously presented $>2\text{ log}_{10}$ IU/mL decrease in HCV RNA from baseline at 12 weeks of therapy but detectable HCV RNA at weeks 12 and 24. Relapsers were defined as patients who achieved an end-of-treatment response but subsequently relapsed and did not achieve an SVR [6].

Therapy was discontinued using the following futility as per stopping rules: in patients whose serum HCV RNA level was >100 IU/mL at treatment week 12, as well as in those who had detectable serum HCV RNA at week 24.

Complete blood counts were obtained prior to treatment initiation and at treatment weeks 4, 8, 12, 24, 36 and 48 and/or at time points where clinically necessary.

Serum HCV RNA levels were also measured at baseline and at the same time points and 24 weeks after treatment discontinuation.

Anemia, neutropenia and thrombocytopenia were graded according to the pivotal studies' grading system [7,8].

Statistical analysis

Statistical analysis was conducted using IBM® SPSS® (Statistical Package for the Social Sciences) Statistics software, version 22. Results are expressed as mean ± standard deviation (SD) or median (range), as appropriate. We applied mainly descriptive statistics and we used Fisher's exact test to detect differences in the probability of SVR between characteristics.

Results

Patients' characteristics

Twenty-six treatment-experienced patients were included in this real-life study. The mean age was 52±14 years while 14 (54%) patients were male and 12 (42%) were female. Almost half (42%) had evidence of cirrhosis, assessed mainly by transient elastography (in 78% of the patients); 38% of the patients had concomitant diseases (hypertension, diabetes mellitus or dyslipidemia). Nearly half of our patients had undetermined previous response with pIFN+RBV (PR) treatment (42%) and 17 (65%) patients had G 1b. Baseline characteristics are shown in Table 1.

Treatment responses and failure

In this study, we recruited 26 patients while 25 of those included in the analysis (one patient lost to follow up during the lead-in period and is unknown if he received even one dose of pIFN alfa + RBV). Nine (36%) of 25 had ≥1log drop of the viral load at week 4. Two of those were relapsers, two

partial responders and five had an undetermined previous response.

Serum HCV RNA was undetectable in 3 patients (12%), 10 patients (40%), 12 patients (48%), and 11 patients (44%) at weeks 8, 12, 24, and 48 (EOT: End of Treatment) respectively. Nine patients (36%) achieved an SVR (Fig. 1).

All patients with SVR had G 1b. Six (67%) of the nine patients with SVR had bridging fibrosis and 3 (33%) had cirrhosis. Five of the nine patients achieved SVR after a decline in serum HCV RNA $\geq 1 \log_{10}$ at week 4 from baseline versus four patients of 16 who succeeded SVR with serum HCV RNA $< 1 \log_{10}$ decline at week 4 (P=0.2). In addition, eight (89%) of the nine patients who achieved SVR had HCV RNA levels < 1000 IU/mL at week 8 and one (6.25%) of the sixteen patients succeeded SVR with HCV RNA levels > 1000 IU/mL at week 8 (P=0.04). As per historical response, 3 of the 5 relapsers, 3 of the 5 partial responders, none of the 5 null responders and 3 of the 11 patients with unknown previous response achieved SVR.

Seven patients (28%) with HCV RNA > 100 IU/mL at week 12 and 3 (12%) with detectable HCV RNA at week 24 stopped treatment (futility rules). Four patients (16%) presented a virological breakthrough (3 of those after week 12 who are the same patients with futility rules at week 24 and 1 patient after week 24) and 2 patients (8%) relapsed following end of treatment with detectable HCV RNA levels at week 72 (Fig. 2).

Safety and tolerability of BOC-based triple therapy

Early treatment discontinuation due to adverse events was observed in 3 (12%) patients during the first three months. One patient (4%) developed grade 4 anemia and neutropenia (Hb < 6.5 g/dL, neutrophils $< 500/\text{mm}^3$). The other 2 patients who discontinued the treatment presented with grade 2 anemia with severe fatigue and infectious diarrhea respectively. There were no deaths during or after the treatment period. Hospitalization was required in two patients (due to grade 4 anemia/neutropenia or diarrhea respectively) while we did not observe any decompensated events.

Table 1 Baseline characteristics of the patients

Characteristic	Patients, n=26
Age (years)*	52±14
Sex (M/F)	14/12
Cirrhosis, n (%)	11 (42%)
Concomitant disease, n (%)	10 (38%)
Genotype (1a/1b)	9/17
HCV RNA, (IU/mL)**	2.65×10^6 (2.85×10^5 - 1.87×10^7)
Hemoglobin, (g/dL)	14.3±0.5
Neutrophils, (K/ μ L)	3.45±1.2
Platelets, (K/ μ L)	193±56
Previous response	
Undetermined response, n (%)	11 (42%)
Relapse, n (%)	5 (19%)
Partial response, n (%)	5 (19%)
Null response, n (%)	5 (19%)

*Mean±SD, **median (range)

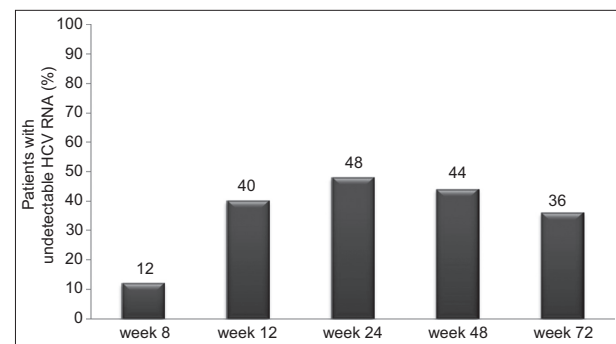


Figure 1 Percentage of the patients with undetectable HCV RNA during treatment and at week 72 (24 weeks after the end of the treatment-sustained viral response)

Side effects of treatment

Twelve patients (48%) experienced at least one episode of anemia (Hb <11 g/dL). In one (4%) patient, Hb levels dropped to a concentration <8 g/dL. The highest decrease in Hb value (mean 2.1 ± 1.7 g/dL) was observed at week 12. None of the patients received erythropoietin, while one patient was hospitalized and received blood transfusion. RBV dose reduction (mean dose reduction 311 mg, range 200-400 mg) was required in 9 (36%) patients (median duration 5 weeks, range 2-34) (Fig. 3)

Sixteen patients (64%) presented with neutropenia (<1500/mm³). Three (12%) patients had grade 4 neutropenia, 4 (16%) grade 3, 3 (12%) grade 2 and 6 (24%) grade 1. The highest decrease in neutrophils (mean 494 ± 336 /mm³) was observed at week 24. Growth CSF was administered in 2 (8%) patients and peg-IFNa dose was reduced in 6 (24%) patients (median duration 11 weeks, range 2-28) (Fig. 4). Two patients (8%) developed thrombocytopenia (<100,000/mm³) and one (4%) had <75,000 platelets/mm³. None of the patients developed bleeding events.

Other adverse events of clinical interest were dysgeusia in twelve patients (48%) and fatigue in 9 (36%). Side effects such as gastrointestinal disorders, diarrhea, fever or flu-like syndrome, dizziness, weight loss, itching, chest pain were reported in <10% of the patients.

Discussion

Since the European Medicines Agency (EMA) approval of BOC in May 2011, patients with CHC G1 and advanced fibrosis/cirrhosis who had previously failed to pIFN+RBV therapy were prioritized on case-by-case need to receive BOC-based triple antiviral therapy, as part of a NPP provided by MSD Greece. This is the first report of safety, tolerability and efficacy of BOC in combination with IFN+RBV in real-life setting of a cohort of these difficult to treat patients in Greece.

According to our results BOC-based regimen in patients with advanced fibrosis and/or cirrhosis found to be safe achieving a SVR rate of 36%. Only 4% (1 patient) had serious adverse events and 12% discontinued treatment. None of the patients developed decompensated liver disease or died. There were 2 hospitalizations due to severe adverse events. Our results are different from the real-life published data from France, Germany and Spain where the investigators reported deaths, cases with liver decompensation or severe uncontrolled infection [21-23]. The different selection criteria might be one possible explanation for the discrepancy. Our patients had well-compensated liver function (albumin >35 g/L and platelets >100,000/mm³). On the contrary, a significant percentage of patients with a history of decompensation in the other cohorts were treated with 1st generation protease inhibitors. The low baseline levels of albumin and platelets were a predictive factor of poor patients' outcome in these studies. An important point was that all patients in tertiary

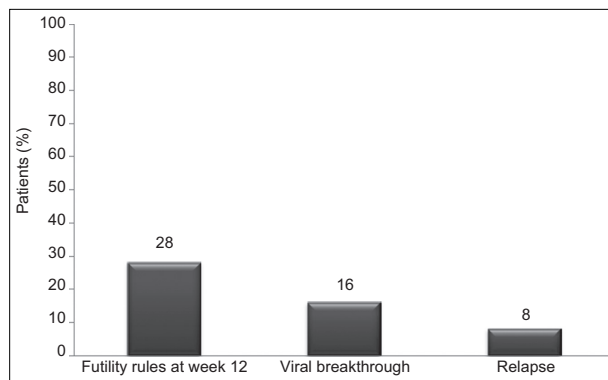


Figure 2 Percentage of patients who did not respond to treatment due to virological breakthrough and relapse or who stopped therapy due to futility rules

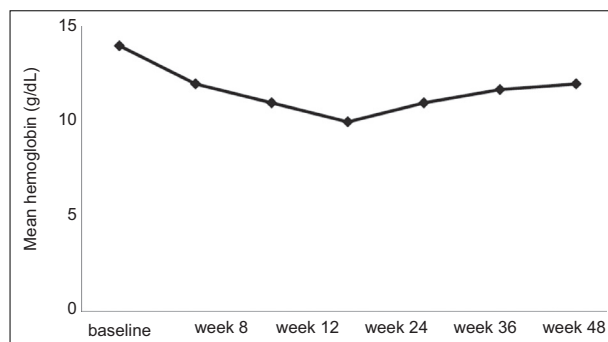


Figure 3 Fluctuation of mean hemoglobin values during treatment. The highest decrease in the mean value was observed at week 12 (mean drop 2.1 ± 1.7 g/dL)

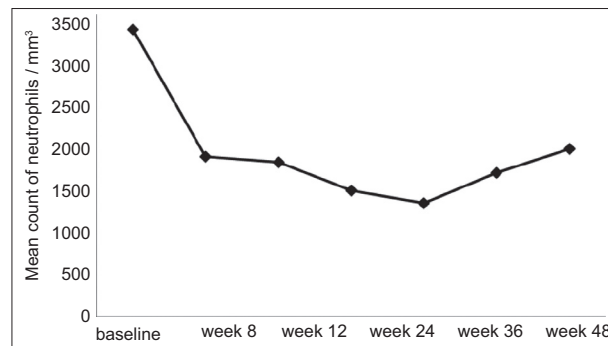


Figure 4 Fluctuation of mean neutrophils' count during treatment. The highest decrease of neutrophils (mean drop 494 ± 336 / mm³) was observed at week 24

Greek centers were closely monitored on a weekly or bi-weekly basis in the clinics. Therefore expert clinicians were able to an early diagnosis of side effects and facilitated a prompt management.

On the other hand, in an Italian study [24] with telaprevir where the participants were patients with bridging fibrosis or cirrhosis and well-compensated liver function the percentage of patients who presented severe adverse events and stopped therapy was similar to ours (16%). Moreover, the results of

the recent HCV-TARGET study [25] revealed a percentage of severe adverse events 13% in the group of patients on BOC. In the last study almost half of the individuals were treatment-experienced and/or cirrhotic.

The most common adverse event requiring management was neutropenia followed by anemia. Almost 2/3 of our cohort developed neutropenia with 28% presenting at least one time with $<750/\text{mm}^3$, a rate consistent to those reported in the RESPOND-2 and PROVIDE studies [8,26]. It is worth mentioning that no severe infections were observed, regardless of the presence of neutropenia. It seems that the severity of liver disease and not the absolute number of neutrophils play the main role in the pathogenesis of infections in these patients [27]. Half of our patients (48%) presented with anemia, as reported previously, and this was managed with RBV dose reduction or in one case (4%) with blood transfusions; none of the patients received erythropoietin since this drug is not indicated for HCV-related anemia under the Greek legislation [21,22].

In this heterogeneous cohort, real-life report in advanced population, SVR rate was 36%. This percentage cannot, however, be compared to those presented in the pivotal studies or in other real-life published studies due to the small number of patients included in the present study. In our cohort, a very small number of patients, only 10% actually, had low levels of baseline serum HCV RNA, in contrast to the 23% of patients with HCV RNA $\leq 800,000$ IU/mL included in the PROVIDE study [26].

All historically null responders in our cohort had $<1 \log_{10}$ decline in the baseline serum HCV RNA concentrations at week 4. The number of the patients who achieved SVR after a 1 log reduction in HCV RNA at week 4 was similar to the number of patients who achieved SVR and had $<1 \log$ reduction in HCV RNA. On the contrary the IDEAL study [5] showed that there is a strong correlation between poor responses to PR therapy at treatment week 4 ($<1 \log_{10}$ decline in baseline HCV RNA) and TW12 ($<2 \log_{10}$ decline from baseline). Notably, we observed that 5 patients, 3 relapsers and 2 partial responders had $<1 \log_{10}$ HCV RNA drop at week 4 compared to baseline, which may indicate that they had changed their profile of IFN response becoming more resistant to IFN over the years. This is of particular significance since 42% of our cohort had an unknown history of previous failure. Resistance to IFN therapy may be a significant reason for the low rate of response in our treatment-experienced population.

Recently, further data analysis from pivotal studies showed that detectable HCV RNA >1000 IU/mL at week 8 of a BOC-based regimen had an excellent negative predictability for SVR achievement [26]. This was evaluated accordingly in all patient types, treatment-naïve, treatment-experienced, cirrhotic, and null, and has now been included in 2014 as the first stopping rule in combination with week 12 and week 24. This new stopping rule as early as week 8 or only 4 weeks of BOC-based therapy will not only save resources from futile treatment in those that are not responding but can also save time and visits for both the clinician and the patient, as well as management of side effects. Our data confirmed the new stopping rule as only one of the 10 patients with HCV RNA

levels >1000 IU/mL at week 8 presented SVR. However, it was noted that the log drop and not the undetectability was the important factor for SVR achievement. Larger number of patients could draw a more substantial conclusion therefore the real-life treatment in Greek conditions could serve such purpose if analysed.

One might argue that we examined a rather small number of patients; however, all patients were with a history of non-response to dual therapy and had advanced disease; they represented a well-studied cohort with close monitoring in a real-life approach.

In conclusion, our data showed that the BOC+pIFN+RBV combination in treatment-experienced adults with advanced liver disease due to HCV G1 infection has a reasonable safety profile, with one in three patients who completed treatment schedule achieving SVR. There were no deaths while all side effects resolved with proper management. Our results also revealed the importance of close monitoring of patients during treatment with 1st generation protease inhibitors and an early diagnosis of the adverse effect.

Cirrhotic patients usually have poor outcomes with an IFN-based regimen. It is clear that these patients should be treated with the newer and safer IFN-free options. Management of cost and not the medical issues will probably be the main point of discussion in the near future.

Summary Box

What is already known:

- Outcomes after retreatment with PR therapy in chronic hepatitis C (CHC) genotype (G) 1 treatment-experienced patients with advanced fibrosis are poor with sustained viral response (SVR) rates of 7-16%
- Triple therapy (PR + protease inhibitor: boceprevir or telaprevir) has improved the SVR rates in this group of patients
- Patients with advanced fibrosis urgently need antiviral therapy due to the risk of progression of the liver disease
- The adverse events of antiviral therapy are more frequent and severe in this group of patients

What the new findings are:

- This study reports the first Greek experience with new triple therapy based on boceprevir regimen
- One in three CHC G1 treatment-experienced patients with advanced fibrosis achieved SVR with a boceprevir-based therapy
- Triple therapy with boceprevir was safe in the group of patients who could tolerate and complete treatment following a good monitoring schedule

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