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Boceprevir in Genotype 1 Chronic Hepatitis C: First Experiences in Serbia

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SUMMARY

Introduction The triple therapy which consists of one of the protease inhibitor plus pegylated interferon and ribavirin (P/R) is the standard of care for the treatment of chronic hepatitis C virus (HCV) genotype 1(G1) infection both in treatment-naïve and experienced patients.

Objective The aim of this study was to analyze the efficacy and tolerability of this regime in hospital practice in Serbia.

Methods From July 2012 to October 2012, 20 previously treated patients with advanced fibrosis and HCV G1 infection were included in the triple antiviral regimen in six referral centers in Serbia. All patients were treated with response guide therapy (RGT) regime according to the boceprevir treatment protocol. During the 4-week lead-in period all patients received peginterferon plus ribavirin. After the lead-in period boceprevir was added in the dosage of 800 mg three times a day orally. The subsequent treatment varied according to virologic response and fibrosis. During the therapy HCV RNA level was measured at week 4, 8, 12, 24 of the treatment for the assessment of virologic response profile. All patients who completed therapy were assessed at the end of the treatment and at the end of an additional 24-week treatment-free period for a sustained virologic response (SVR).

Results The total of 20 patients with advanced fibrosis was treated. Among patients with an undetectable HCV RNA level at week 8 the rate of SVR was 100%. No patient with decrease in the HCV RNA level <1 log 10 IU/ml at treatment week 4 achieved SVR. The overall rate of SVR was 55%. The safety profile of the treatment regimen was good. Anemia was reported in 25% of patients. There was no life-threatening treatment adverse event.

Conclusion Boceprevir in combination with P/R achieved fairly good SVR rates in patients that were "most difficult to treat" who failed on dual therapy and was effective among patients with cirrhosis.

Keywords: chronic hepatitis C; protease inhibitor; boceprevir

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is a global health concern affecting up to 170 million people worldwide. HCV infection is the leading cause of liver-related morbidity and mortality [1, 2, 3]. The combination therapy of pegylated interferon (PEG-IFN) and ribavirin (RBV) has been available since early 2000 and is the standard of care for more than 10 years. Unfortunately this therapy is effective in 40–50% of genotype 1-infected patients [4, 5]. In treatment failure, infection may progress to the end-stage liver disease, hepatocellular carcinoma and liver failure. After the end-stage liver disease is established the only reliable therapeutic intervention is liver transplantation. The antiviral agents specifically targeting either the HCV protease or polymerase, or other targets, are now in clinical development [6, 7, 8]. When the first direct-acting antiviral agents (DAAs) entered clinical trials with HCV-infected patients, the hope has risen that they might replace PEG-IFN and/or RBV therapy by displaying potent viral suppression. However, early clinical trials showed that the DAA monotherapy was associated with emergence of resistance mutations within a week, and as such, should not be given alone [8, 9]. Boceprevir, DAA of the first generation is a linear peptidomimetic ketoamide serine protease inhibitor that binds reversibly to the HCV nonstructural 3(NS3) active site. Boceprevir demonstrated antiviral activity in phase 2 studies of both, patients infected with HCV genotype 1 who did not receive prior treatment and in those pretreated [10, 11]. In 2011, the HCV protease inhibitor of the first generation boceprevir entered the market to be used in combination with PEG-IFN and RBV for genotype 1 HCV infection. This triple antiviral therapy suppresses viral breakthrough and increases

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the likelihood of sustained virologic response (SVR). Yet these agents drive selective pressure for mutant viruses that can reduce susceptibility to any given drug. DAAs also result in adverse events in a proportion of patients, adding concerns of tolerability that exist with PEG-INF and RBV. Using DAAs in clinical practice has raised important issues related to the duration of treatment, early stopping rules, retreatment of previously treated patients, and how or when DAA should be combined [12].

OBJECTIVE

The aim of this study was to analyze the efficacy and tolerability of boceprevir in combination with PEG-IFN and RBV in treating chronic HCV genotype 1 infection in a real world setting of Serbian tertiary referral centers.

METHODS

Patient selection

Six referral centers in Serbia participated in the study. The protocol was signed by investigators and approved by an independent ethics committee. All patients provided written informed consent prior to conducting any procedures. Institutional database was used to identify patients eligible for the study. Baseline data included patient demographics, previous antiviral therapy and hepatic fibrosis according to the Metavir scoring system. Twenty adult 18-65 years old interferon experienced patients, who had chronic HCV infection genotype 1, quantifiable HCV RNA and histologically proved chronic hepatitis or cirrhosis, were included in the triple antiviral regime in the period July–October 2012. The exclusion criteria were liver diseases of other cause, decompensated cirrhosis, renal insufficiency, coinfection (HIV and hepatitis B infection), pregnancy, current breast-feeding, active cancer, active substance abuse and severe psychiatric disorders.

Study design

The primary objective was to analyze the efficacy and safety of the triple therapy containing boceprevir in combination with pegylated interferon alfa-2a or 2b and ribavirin in real clinical practice in Serbia. For the purpose of the study doses of pegylated IFN alf-2a were administrated subcutaneously at a dose of 180 mcg once a week while pegylated interferon alfa-2b was administrated subcutaneously at a dose of 1.5 mcg per kilogram of body weight once a week. Ribavirin was administrated at a divided daily dose of 800 to 1200 mg on the basis of body weight. The treatment with boceprevir consisted of oral administration at a dose of 800 mg three times a day (to be taken with food and with an interval of 8 hours between the doses) in four capsules of 200 mg each. All patients were treated with response guide therapy (RGT) regimen according to the boceprevir treatment protocol presented in Figure 1. During the 4-week lead-in period all patients received peginterferon plus ribavirin (P/R). The subsequent treatment varied according to virologic response and fibrosis. Patients with an undetectable HCV RNA level at week 8 and 12 received boceprevir plus P/R for 32 weeks and completed therapy at week 36, whereas those with a detectable HCV RNA level at week 8 (but undetectable level at week 12) received P/R for additional 12 weeks. Patients with cirrhosis received boceprevir plus P/R for 44 weeks. All patients were under follow-up for the next 24 weeks after therapy completion. The stopping rule applied in all patients was failure to achieve HCV RNA level at week 12 less than 100 IU per milliliter or an undetectable HCV RNA level at week 24. These stopping rules resulted in discontinuation of all treatment and advancement to follow-up.

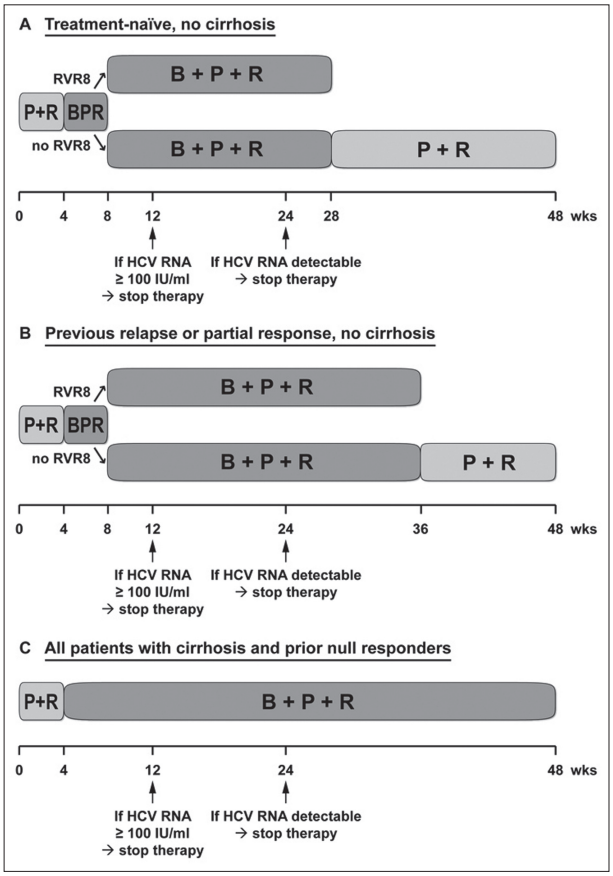

Figure 1. Boceprevir-based triple therapy: (A) Treatment-naïve patients with CHC of genotype 1 without cirrhosis; (B) Treatment-experienced patients with CHC genotype 1 and previous relapse or partial response without cirrhosis; (C) All cirrhotic patients and prior null responders.

B – boceprevir; BPR = B + P + R; P – pegylated interferon-α; R – ribavirin; RVR8 – undetectable HCV RNA at week 8; wks – weeks

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Laboratory tests, including the assessment of plasma HCV RNA levels and serum ALT activity, viral genotyping and histological evaluation were performed at central laboratories of the Clinical Centre of Serbia. Pretreatment biopsy specimens were evaluated by the hepatopatholo-

gist from the Institute of Pathology, Faculty of Medicine, University of Belgrade. During the therapy the HCV RNA level was measured at week 4, 12, 24 of the treatment for the assessment of virologic response profile. The HCV RNA level was measured at week 8 of the treatment as well, so as to assess its predictive value although this procedure was not mandatory according to the boceprevir treatment protocol. The most important results were the HCV RNA level at week 4 and 8 because of its predictive value. The 4-week lead-in period of peginterferon-ribavirin treatment allowed the assessment of interferon responsiveness and its relationship to sustained virologic response. It is well known that patients with poor response to IFN defined as a reduction in the HCV RNA level of less than 1 $\log_{10}$ IU per milliliter after week 4 of P/R therapy, were less likely to have SVR after boceprevir was added than patients with a robust response to IFN. HCV RNA level at week 8 was especially important as a newly recognized predictor of SVR. The data collected from the real life setting showed that failure to suppress viral load below 1000 IU per milliliter at week 8 was an indicator of poor outcome allowing promotion of new stopping rule in future.

Assessment of safety and efficacy

Safety was assessed through physical examination and monitoring of adverse events (AEs) and laboratory abnormalities. The adverse events were graded as mild, moderate, and severe or potentially life-threatening. Every change was recorded at week 1, 2, 4 of the study and every 4 weeks during the treatment. Non-life threatening hematologic adverse events were managed by means of P and/or R dose reduction. The decisions were made at the discretion of the investigators. In the follow-up period clinic visits were scheduled at 12 week intervals. Patients with AEs or important abnormalities in laboratory values received lower doses of P/R (25%, 50%, or 75% reduction in the assigned dose). According to the protocol, the dose of boceprevir was not reduced during treatment.

The primary efficacy endpoint was SVR defined as an undetectable plasma HCV RNA level at week 24 of the follow-up period. Relapse was defined as the occurrence of detectable HCV RNA level at the end of treatment but detectable HCV RNA level at some point during the follow-up period.

Statistical analyses

All patients who received at least one dose of study medication were included in all efficacy analyses and if they had at least one post-baseline safety assessment, they were included in the safety analysis. Continuous variables with normal distribution were expressed as mean and standard deviation, and variables with skewed distribution as median and range. Baseline categorical variables were compared by the Pearson's χ^2 test, and continuous variables were compared by the Mann-Whitney U-test. A multiple logistic regression model was used to explore baseline predictive factors of SVR. Statistical significance was taken as $p<0.05$.

RESULTS

Characteristics of the patients

Characteristics of the patients at baseline are summarized in Table 1. The mean age was 48.6 years and the mean body weight was 78.5 kg. The majority of patients were male (65%) and with unknown risk for HCV transmission (50%). At the baseline visit 75% of patients had a high viral load (HCV RNA level >800,000 IU/ml). All patients had advanced fibrosis according to the Metavir score system (3 or 4). A total of 50% of patients had cirrhosis as presented in Table 2. All patients were experienced patients with various sorts of unsustainable response. Most of them were relapsers (Table 3). Baseline serum ALT levels were elevated in all patients but no patient had ALT levels more than five times higher than the normal upper limit.

Table 1. Baseline demographic data on 20 patients from 6 referent centers for HCV in Serbia, and disease characteristics of genotype 1 chronic hepatitis C treated by triple therapy B+P+R

Characteristics		Value
Gender	Male	13 (65%)
	Female	7 (35%)
Mean age (years)		48.6 (±10.6)
Mean weight (kg)		78.5 (±14.3)
Mode of transmission	Transfusion	4 (20%)
	IVDU	2 (10%)
	Surgery or other medical intervention	2 (10%)
	Hemophilia	1 (5%)
	Acciden injury	Unknown
	Unknown	10 (50%)

The values are expressed as mean value with standard deviation, and the number of patients with percentage.
B – boceprevir; P – pegylated interferon; R – ribavirin); IVDU – intravenous drug user

Table 2. Baseline disease characteristics (genotype 1 chronic hepatitis C)

Characteristics		Value
Viral load	>800,000	16 (75%)
	<800,000	4 (25%)
Fibrosis score	F3	10 (50%)
	F4	10 (50%)
HCV infection duration (years)		7.7 (±4.6)

The values are expressed as mean value with standard deviation, and the number of patients with percentage.

Table 3. Characteristics of previous treatment and response

Characteristics		N
Therapy	Peg IFN alfa-2a + Ribavirin	20 (100%)
	Peg IFN alfa-2b + Ribavirin	0 (0%)
Previous treatment response	Relapsers	14 (70%)
	Non-responders	4 (20%)
	Null responders	1 (5%)
	Partial responders	1 (5%)

N – number of patients

Efficacy

Viral kinetic during the treatment is presented in Graph 1. None of the patients with HCV RNA level >1000 IU/mil at week 8 achieved SVR. All patients who achieved SVR did not have either undetectable HCV RNA at week 12 or a decrease of viral load for more than two logs. These patients had a normal ALT level at the end of the follow-up period as well.

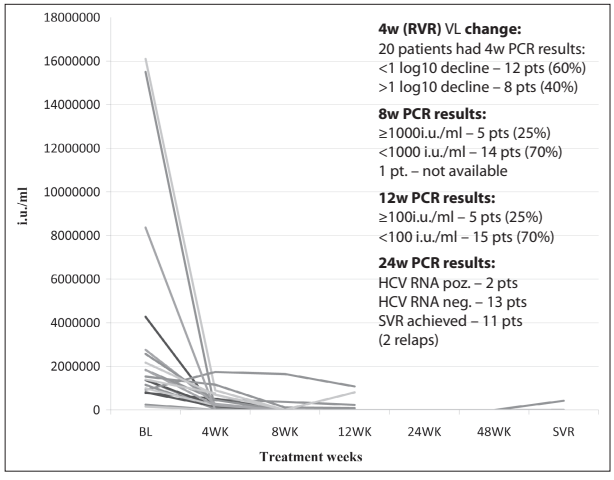
The virologic response at the end of the therapy was achieved in 13(65%) patients and in 11(55%) patients at the end of the follow-up period respectively as presented in Graph. 2. The main reasons for withdrawal of boceprevir were poor viral response and/or comorbidities. In five patients boceprevir was interrupted at week 12 due to the stopping rule. At week 24 we recorded breakthrough in two patients. In these patients also boceprevir was interrupted according to the stopping rule. One of these patients experienced liver decompensation as well.

Neither partial nor null responder achieved SVR. The best results were recorded in relapsers (approximately 70%). The rates of SVR by previous treatment response are presented in Graph 3.

Treatment with boceprevir plus P/R was consistently associated with higher rates of SVR among patients with fibrosis 3 (70%) than in patients with cirrhosis defined as "difficult-to-treat" patients (40%). The rates of SVR by HP finding are presented in Graph 4.

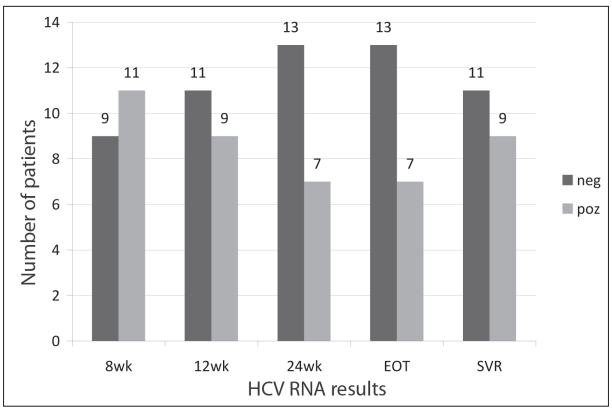
Safety

In general, therapy was going well. The most commonly reported events were dysgeusia, fatigue, mild depression, loss of appetite and fever. Table 4 summarizes the adverse events that were reported during the treatment. Ribavirin dose modification (defined as reduction or omission of one or more doses of the study medication) was necessary in five patients because of anemia. Two of them were treated with blood transfusions. In most of the patients

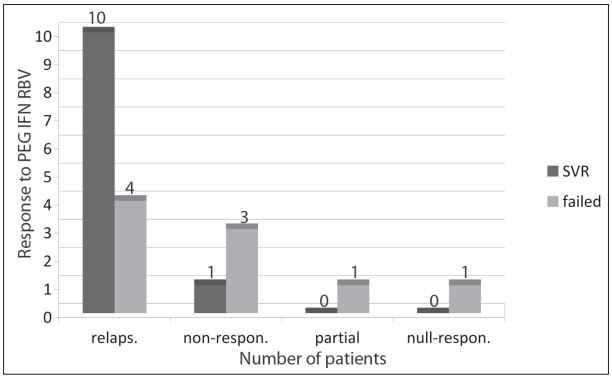


Graph 1. Viral kinetics

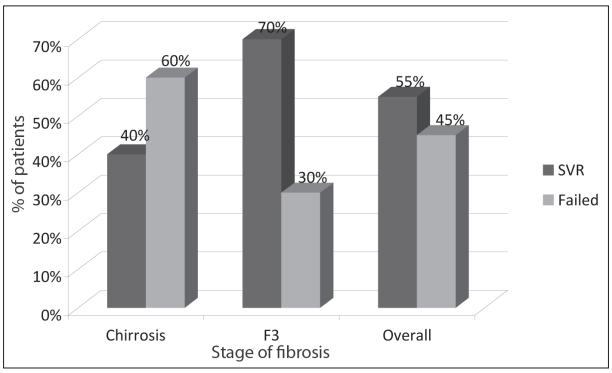
VL – viral load; PCR – polymerase chain reaction; RVR – rapid virologic response; pts – patients; HCV RNA – hepatitis C viral ribonucleic acid



Graph 2. Results of PCR testing during treatment



Graph 3. Treatment outcome according previous treatment response to PEG IFN RBV



Graph 4. Treatment outcome according stage of fibrosis

Table 4. Safety results: summary of adverse events

Adverse events	N	Comments
Dysgeusia	8	Annoying, but not debilitating
Fatigue	2	Mild degree
Mild depression	1	Not required medication
Apetite loss	1	
Fever	1	At first week of treatment
Anemia	2	Treated with blood transfusion
	3	Treated with RBV dose reduction
Neutropenia $<0.75\times10^9$/l	1	Treated with PEG IFN dose reduction
Thrombocytopenia $<50\times10^9$/l	1	Treated with PEG IFN dose reduction
Death	0	
Life-threatening treatment-emergent AE	1	Liver decompensation

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thrombocytopenia and/or neutropenia were recorded to some extent during the treatment but only in two patients PEG-IFN dose reduction was necessary. Treatment was discontinued in one patient because of liver decompensation. None of the patients died either during therapy or follow-up period.

DISCUSSION

To date most of evidence pertaining to boceprevir plus P/R efficacy has been derived from controlled trials [10, 11]. The outcomes from such studies are often better than what can be achieved in routine clinical practice as a consequence of the selection of patients, increased monitoring support and improved compliance. Given the expectation of poor tolerability, the level of response that can be expected in non-trial settings is quite clear. Therefore, we studied a cohort of patients treated in the setting of routine clinical care in order to address these differences. In this multicenter study the so-called "difficult-to-treat" patients including those with advanced liver disease, patients with previous treatment failures and patients with comorbidities were included. Selection of patients for treatment was based on several factors that included treatment urgency, treatment-associated safety concerns and chance for SVR. On the other hand safety concerns played the major role for not selecting patients for therapy. There are potential limitations of this study which deserve to be mentioned. First of all it is a small sample size which did not allow comparison between different duration of therapy and previous treatment response. Second, due to technical reasons some data are missing such as HCV RNA result at week 8 for one patient. Another possible limitation concerns the stratification of patients according to fibrosis. In some patients a liver biopsy sample was taken more than five years ago. A patient tested negative for cirrhosis five years before the triple therapy, could develop cirrhosis in the intervening years. Thus patients with cirrhosis could have been mischaracterized as being non-cirrhotic.

The overall rate of SVR was 55%. Significantly better rates of SVR were achieved in the group of previous relapsers (with notable responsiveness to IFN) than the group consisting of null, partial and non-responders (72% vs. 16%). The 4-week lead-in period of peginterferon-ribavirin treatment was very important phase. This phase allowed for the assessment of interferon responsiveness and its relationship to sustained virologic response [10, 11, 13, 14]. Patients with poor response to IFN defined as a reduction in the HCV RNA level of less than 1 $\log_{10}$ IU per milliliter after week 4 of P/R therapy were less likely to have SVR after boceprevir was added than patients with a robust response to IFN [10, 15]. The lead-in period was important to test both compliance and tolerability and to decrease HCV RNA levels before exposure to boceprevir, thereby reducing the risk of viral breakthrough or resistance to boceprevir [10, 11, 16]. The virologic response during the lead-in period could help to predict the best possible treatment duration because it can identify null responders to P/R who seem to be at the greatest risk for treatment failure and for the development of resistance. At week 4 60% of patients had viral load decline<1 $\log_{10}$ IU per milliliter which was associated with a lower rate of SVR. Rapid virologic response (undetectable HCV RNA level at treatment week 4) was achieved only in one patient. The predictive value of "on treatment" markers such as the week 8 HCV viral load was studied. Patients who had HCV RNA<1000 IU per milliliter at week 8 were more likely to go on to SVR. We found that the failure to suppress viral load below 1000 IU per milliliter at week 8 was an indicator of poor outcome. The week 8 was passed by 14 (70%) patients with the HCV RNA level<1000 IU per milliliter. From this group 11 (78%) patients achieved SVR. Nine patients had undetectable HCV RNA level. Furthermore, all patients with HCV RNA level>1000 IU per milliliter at week 8 did not pass stopping rule at week 12. Although the number of patients was small this indicated a predictive value of HCV RNA testing at week 8. Estimating new stopping rule at week 8 could be useful and cost benefitial [15, 17]. The stopping rule at week 12 was passed by 15 (75%) patients. From this group 11 patients passed week 12 with undetectable HCV RNA levels. As expected, all patients with undetectable HCV RNA level at week 12 achieved SVR.

In the group of non-responders (patients with unclassified or non-sustainable response) only one of four patients achieved SVR. Our data showed a significantly higher rate of SVR in patients with F3 fibrosis, than in patients with F4 (70% vs.40%) which confirmed that the lower stage of fibrosis is the major predictor for successful treatment [10, 11, 17, 18, 19]. Safety profile was also better in F3 group of patients. Furthermore the rate of SVR in patients with cirrhosis actually did not differ from the standard of care regime [20, 21]. According to the poor outcome of patients with cirrhosis (40%) it was concluded that despite improvement achieved during the last 3 years, safer and more efficient treatment options are still urgently needed. Due to a small sample size it was not possible to confirm the predictive value of other baseline variables in our study.

Concerns relating to AEs and poor tolerability are cited as a barrier to the use of boceprevir plus P/R in patients with cirrhosis [22]. Although our cohort included a significant proportion of patients with cirrhosis, we found boceprevir plus P/R to be well tolerated with 65% of patients able to complete therapy. The management of AEs was a demanding job. The treatment required significant resources both in terms of time and monitoring visits as well as in terms of management of side effects. The patients were seen almost every week at our outpatient clinics and the overall frequency of consultations was certainly considerably higher since we did not assess visits at the general practitioner office and local hospitals. The regime that included boceprevir plus P/R was associated with increased rates of anemia (25% of patients) with hemoglobin level<9.5 per deciliter. The rates of anemia were not higher than among patients with standard care but the severity of anemia was higher and required hospitalizations in few patients [10, 22]. Despite severe anemia in two patients, there was no

treatment discontinuation because of anemia. Anemia was usually managed with RBV dose reduction except in two patients who needed blood transfusion. Hospitalization was necessary only in three patients (two because of anemia and one because of liver decompensation). Similar rates of anemia were reported in patients with compensated cirrhosis and bridging fibrosis. This discrepancy can be accounted for by a small number of patients. Another reason could be outdated results of liver biopsy and therefore actually a higher rate of unrecognized cirrhosis. Not unexpectedly, anemia more often occurred in patients older than 60 years and low pretreatment Hgb values [10, 21].

In contrast to the registration trials, a higher proportion of patients had to stop therapy prematurely [10, 11]. Both virologic treatment failure and adverse events accounted for these early treatment discontinuations. The main reasons for virologic failure might be the advanced liver disease and previous treatment failure. Only one patient had to prematurely discontinue the treatment owing to liver decompensation. In contrast to pivotal registration trials, safety and efficacy of this antiviral regimen are limited in a real clinical practice [22].

Even a small sample size results allowed insight that best candidates for boceprevir plus P/R treatment are relapsers with F3 fibrosis. Response rates in patients with cirrhosis are unsatisfactory but the small sample did not allow consistent conclusions. On the other side, the safety profile was satisfactory even in patients with cirrhosis. Nevertheless, the SVR results need to be confirmed in a long-term follow-up. In most countries treatment of naïve patients with advanced fibrosis has been prioritized so as to receive the triple therapy but our results also provide encouraging although preliminary data of the efficacy of boceprevir triple therapy in the treatment of experienced patients with bridging fibrosis and cirrhosis. These findings were particularly rewarding for those individuals with a previous relapse to P/R. Our observation and results are not in line with the CUPIC study even though all patients were experienced patients [10, 22]. AEs in our patients were much lower and no one died. Relatively low rates of AEs are related to excellent patient compliance and close monitoring. One important limit of the CUPIC study is the underrepresentation of null responders who are most difficult to cure as a consequence of their poor IFN sensitivity leading to a high risk of virologic breakthrough and post-treatment relapse of HCV infection. High efficacy of PI-based therapies in registration trials raises high ambition to treat a great number of patients which may lead to an underestimation of risk factors. In our opinion patients need to be selected very carefully to ensure a reasonable safety profile and a high efficacy. Generally speaking our results showed that efficacy was worse than in registration studies but the safety profile was much better than in the CUPIC study [10, 12, 22].

CONCLUSION

Our study provides a "real world" and encouraging data concerning safety, tolerability and clinical effectiveness of boceprevir plus P/R treatment in clinical practice of Serbia. Evaluating 20 patients we found that the best candidates for boceprevir plus P/R treatment are previous relapsers and those with F3 fibrosis and well compensated cirrhosis with some positive predictors for SVR (good response to IFN and without comorbidities). By including more easier-to-treat patients the great effort that is required for therapy management would be reduced. More balanced patient group may permit more cost-effective treatment of a higher number of HCV infected people.

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Боцепревир у хроничном хепатитису Ц генотип 1: прва искуства у Србији

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КРАТАК САДРЖАЈ

Увод Тројна антивирусна терапија коју чине један инхибитор протеазе, пегиловани интерферон и рибавирин (П/Р) стандардна је терапија за лечење хроничног хепатитиса Ц (ХЦВ) генотип 1 (Г1) код болесника који раније нису лечени, као и код претходно неуспешно лечених особа.

Циљ рада Циљ истраживања је била анализа ефикасности и подношљивости овог режима у стварној клиничкој пракси у Србији.

Методе рада Од јула до октобра 2012. године 20 претходно лечених болесника са напредовалом фиброзом и ХЦВ Г1 инфекцијом укључено је у режим тројне антивирусне терапије у шест референтних центара у Србији. Сви испитаници су лечени применом режима „одговором вођене терапије“ (ОВТ) у складу с терапијским протоколом за боцепревир. Код свих болесника је започета примена П/Р током четири недеље уводног периода. Након овог периода у терапију је додат боцепревир у дози од 800 милиграма три пута дневно орално. У даљем току лечење је зависило од вирусолошког одговора и степена фиброзе. Ради провере профила вирусолошког одговора, мерен је ниво ХЦВ РНК у 4, 8, 12. и 24. седмици терапије. По завршетку лечења и након 24 седмице клиничког праћења, код свих испитаника је проверено да ли су постигли стабилан вирусолошки одговор (СВО).

Резултати Лечено је укупно 20 болесника од којих је 50% имало цирозу јетре. Међу испитаницима са недетектибилном ХЦВ РНК у 8. недељи лечења стопа СВО је била 100%. Од болесника код којих је забележено смањење нивоа ХЦВ РНК*<1 log 10 IJ/ml* након четири седмице лечења нико није постигао СВО. Укупна стопа СВО била је 55%. Сигурносни профил режима је добар. Анемија је установљена код 25% испитаника. Није било нежељених догађаја који би угрозили живот болесника.

Закључак Боцепревир у комбинацији са П/Р доводи до постизања значајне стопе СВО код болесника који су претходно неуспешно лечени двојном терапијом и ефикасан је код болесника с цирозом јетре који се сматрају најтежим за лечење.

Кључне речи: хронични хепатитис Ц; протеазни инхибитор; боцепревир

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