

Original paper

Efficacy and direct costs of chronic hepatitis C treatment with first generation NS3/4A protease inhibitors in a real life population

Anna Piekarska¹, Ewa Koślińska-Berkan¹, Kamila Wójcik¹, Anna Skubała¹, Maciej Jabłkowski², Zbigniew Deroń³, Aleksandra Berkan-Kawińska¹

¹Department of Infectious Diseases and Hepatology, Medical University of Lodz, Poland

²Department of Infectious and Liver Diseases, Medical University of Lodz, Poland

³Observation – Infectious and Hepatology Department, Bieganski Voivodship Specialist Hospital in Lodz, Poland

Abstract

Introduction: Recent years have brought a significant advance in chronic hepatitis C (CHC) treatment that includes development of direct acting antivirals (DAA). Two of them, boceprevir (BOC) and telaprevir (TVR), were first approved for treatment of patients infected with CHC genotype 1 in combination with pegylated interferon (P) and ribavirin (R). Our aim was to evaluate the efficacy and direct costs of BOC/PR and TVR/PR in a real life population.

Material and methods: The study included adult patients qualified for the CHC Therapeutic Programme treated with TVR/PR or BOC/PR. Treatment was continued for 24 or 48 weeks. Sustained virological response, treatment discontinuation due to adverse events and lack of virological response rates were compared.

Results: A total of 243 adult patients with CHC were included. TVR/PR and BOC/PR were administered in respectively 122 and 121 patients. Thirty-two patients (13%) were treatment-naïve, whereas liver cirrhosis/advanced fibrosis was observed in 138 patients (56.7%). Overall, 43.6% of patients achieved a sustained virologic response (SVR). In the BOC/PR group the SVR rate was significantly lower than in the TVR/PR group (33.1% vs. 54.1%; $p = 0.00094$). Lack of response to therapy was observed in 41.3% and 12.3% of patients receiving BOC and TVR, respectively ($p < 0.00001$). The direct cost of achieving SVR in one patient was 285 450 PLN with BOC and 185 757 PLN with TVR.

Conclusions: The very low treatment efficacy may be the result of inclusion criteria that allowed treatment of patients with advanced liver fibrosis/liver cirrhosis or previous treatment failure. Telaprevir seems to be significantly more potent against hepatitis C virus, with similar safety and tolerance.

Key words: hepatitis C, boceprevir, first-generation protease inhibitors, sustained virologic response, telaprevir.

Address for correspondence

Aleksandra Berkan-Kawińska, Department of Infectious Diseases and Hepatology, Medical University of Lodz, 1/5 Kniaziewiczza St., 91-347 Lodz, Poland, phone: +48 661 191 396, e-mail: aleksandra.berkan@gmail.com

Introduction

Chronic hepatitis C (CHC) persists as a major epidemiological issue in Poland. According to Polish Expert Group estimates approximately 0.6% of the whole Polish population may be chronically infected with hepatitis C virus (HCV) [1]. Recent years have brought a significant advance in CHC treatment that includes

development of direct acting antivirals (DAA). First generation DAA – NS3/4A protease inhibitors – were included in the National Therapeutic Programme for Hepatitis C in 2013. Two of them (boceprevir [BOC] and telaprevir [TVR]) were approved by the European Medicines Agency and reimbursed by the Polish Ministry of Health for patients infected with HCV genotype 1 in combination with interferon and ribavirin. Results of

clinical trials (boceprevir/pegylated interferon/ribavirin [BOC/PR] and telaprevir/pegylated interferon/ribavirin [TVR/PR]) were encouraging – the new agents seemed to exhibit very strong antiviral activity that exceeded the efficacy of dual therapy based on pegylated interferon and ribavirin (PR), with the sustained viral response (SVR) ranging from 66 to 75% [2-4].

Nevertheless, the high antiviral potential of BOC and TVR reported in clinical trials was observed mostly in naïve patients (only if IL-28B TT polymorphism was present), as well as in patients with a low fibrosis stage (F0-F2 on the METAVIR scale). However, according to the National Therapeutic Programme for Hepatitis C, NS3/4A protease inhibitor-based therapy was available only in treatment-experienced patients with a fibrosis stage of at least F2. Such eligibility criteria limited treatment expenses nationally, but resulted in decreased cost-effectiveness and augmented risk of serious adverse events observed especially in patients with liver cirrhosis [5].

Our aim was to evaluate the efficacy of first generation protease inhibitors in patients with CHC and to compare the direct costs of BOC/PR and TVR/PR therapies in a real life population.

Material and methods

Inclusion criteria

The following analysis is a retrospective evaluation of efficacy and direct costs of BOC/TVR-based therapies in patients qualified for the Hepatitis C Therapeutic Programme valid at the moment of study (currently replaced by an interferon-free regimen) within routine clinical practice. The study included adult patients treated with TVR/PR or BOC/PR who completed a 6-month follow-up after treatment.

Inclusion criteria were as follows:

- 1) chronic hepatitis C infection (positive serum anti-HCV antibodies, detection of HCV RNA in serum/liver),
- 2) HCV genotype 1 infection,
- 3) age \geq 18 years,
- 4) treatment-experienced patients (treatment-naïve only if IL-28B TT polymorphism present),
- 5) liver fibrosis confirmed with liver biopsy or transient elastography in patients with contraindications to liver biopsy: \geq F2 in treatment-naïve or \geq F1 in treatment-experienced (PR therapy) patients.

The exclusion criteria were as follows:

- 1) patients with clinical manifestations of liver failure (liver cirrhosis of classes B and C according to the Child-Pugh classification),
- 2) contraindications to interferon therapy,

- 3) severe concomitant diseases (severe cardiovascular disease, poorly controlled diabetes, autoimmune diseases, hyperthyroidism, retinopathy, drug-resistant epilepsy, severe psychosis, active neoplastic disease),
- 4) active alcohol and/or psychoactive drug abuse,
- 5) pregnancy and lactation,
- 6) HIV/HBV coinfection,
- 7) positive history of liver transplant.

Medication

Boceprevir was administered in a dose of 800 mg three times daily whereas TVR was administered in a dose of 1125 mg twice a day, both in combination with pegylated interferon alfa-2a or alfa-2b and ribavirin. The standard dose of pegylated interferon alfa-2a was 180 μ g per week and the standard dose of pegylated interferon alfa-2b was 1.5 μ g per kilogram per week. The baseline ribavirin dose was 1200 mg in patients with body weight $>$ 75 kg and 1000 mg in patients with body weight $<$ 75 kg. Treatment was continued for 24 or 48 weeks. Length of the therapy and indications to treatment discontinuation due to lack of virological response were determined in accordance with the Summaries of Product Characteristics for TVR and BOC.

Methods

Demographic data were collected retrospectively using a database that included all patients treated with BOC or TVR. Anti-HCV antibodies were tested by a third-generation enzyme-linked immunoassay (ELISA). HCV RNA was assessed by the reverse transcription PCR (RT-PCR) method with COBAS AMPLICOR HCV v. 2.0 (Roche Diagnostic Inc.). The lower limit of detection was 15 IU/ml. HCV genotype was determined by a hybridization method (InnoLipa HCV, Innogenetics). Quantitative serum HCV RNA was assessed in all patients at baseline, at weeks 4, 12, 24 and at the end of treatment. Early virological response (EVR) was defined as undetectable HCV RNA after 12 weeks of treatment. Lack of response to treatment was diagnosed when the serum HCV RNA level remained above the limit of detection throughout the therapy. The efficacy end point was sustained virological response (SVR), defined as undetectable HCV RNA at 24 weeks after the end of treatment.

Liver biopsy was performed in 52 patients and a histological evaluation was carried out according to the METAVIR classification system. Transient elastography was performed in patients according to the manufacturer's instructions (FibroScan, Echosens).

The results were expressed in kilopascals (kPa) applying the following cut-off values to determine the degree of fibrosis [6]: < 7.5 kPa – mild or no fibrosis (F0-F1); 7.5 kPa and < 9.5 kPa – significant fibrosis (F2); ≥ 9.5 kPa and < 12.5 kPa – severe fibrosis (F3); ≥ 12.5 kPa – liver cirrhosis (F4).

The variables were compared between patients with SVR and those without as follows: type of treatment (TVR vs. BOC), stage of fibrosis and history of interferon treatment. In patients without SVR we further compared the rates of treatment discontinuation due to adverse events or lack of virological response.

The cost of medications was estimated based on their invoice prices financed by the National Health Fund. The amount of medications used by each patient until treatment end/discontinuation was calculated. The costs of other services provided within the National Therapeutic Programme for Hepatitis C were not included in the analysis.

Statistical analysis

Quantitative data were presented as mean and median. Qualitative data were characterised by number and percentage distribution and assessed by Pearson's χ^2 test. Statistical significance was accepted as $p < 0.05$.

Results

Safety and efficacy

A total of 243 adult patients with chronic hepatitis C genotype 1 (138 men and 105 women aged 22-76, mean age: 49.2 years) who received antiviral treatment between July 2013 and June 2016 in Biegański Hospital in Lodz according to the criteria of the National Therapeutic Programme for Hepatitis C were included in the study. Patients finished antiviral treatment and 24 weeks of follow-up. TVR/PR and BOC/PR were administered in respectively 122 and 121 patients.

Thirty-two patients (13% of the whole study population) were treatment-naïve, whereas 211 patients (87%) experienced failure of previous pegylated interferon and ribavirin therapy. Rates of treatment-experienced patients in BOC and TVR groups were respectively 90.1% and 83.6%. Liver cirrhosis or advanced liver fibrosis (F3/F4) was observed in 138 patients (56.7%), while mild liver fibrosis (F1/F2) was observed in 105 patients (43.3%). In BOC-treated and TVR-treated groups liver cirrhosis or advanced fibrosis was observed in respectively 60.3% and 53.3% of patients.

The differences in age, sex, history of treatment and fibrosis observed between the two groups were statisti-

cally insignificant. Baseline characteristics of the study population are presented in Table 1.

Overall, 43.6% (106/243) of patients achieved an SVR. In the BOC/PR group the SVR rate was significantly lower than in the TVR/PR group (33.1% [40 patients] vs. 54.1% [66 patients]; $p = 0.00094$). A statistically significant difference in SVR rates was also observed in a subgroup of patients with advanced liver fibrosis, who responded significantly better to TVR than to BOC (52.3% vs. 27.4%, respectively; $p = 0.00276$).

Similarly, SVR rates among treatment-experienced patients were significantly higher in the TVR/PR group – 53.9% vs. 34.9% in the BOC/PR group

Table 1. Baseline characteristics of the study population

Factor	Telaprevir	Boceprevir	<i>p</i>
Number of patients	122	121	
Age			
Mean	47.4	51.0	
Median	51	55	0.059998
Range	22-74	22-76	
Sex, <i>n</i> (%)			
Women	49 (40.2%)	56 (46.3%)	0.33582
Men	73 (59.8%)	65 (53.7%)	
History of treatment, <i>n</i> (%)			
Naive	20 (16.4%)	12 (9.9%)	0.13552
Experienced	102 (83.6%)	109 (90.1%)	
Liver fibrosis, <i>n</i> (%)			
Low (F0-2)	57 (46.7%)	48 (39.7%)	0.26719
Advanced (F3-4)	65 (53.3%)	73 (60.3%)	

Table 2. Treatment outcomes in the study groups

Factor	Telaprevir	Boceprevir	<i>p</i>
SVR rates, <i>n</i> (%)			
Overall	66 (54.1%)	40 (33.1%)	0.00094
History of treatment			
Naive	11 (55%)	2 (16.7%)	0.03256
Experienced	55 (53.9%)	38 (34.9%)	0.00533
Liver fibrosis			
Low (F0-2)	32 (56.1%)	20 (41.7%)	0.13948
Advanced (F3-4)	34 (52.3%)	20 (27.4%)	0.00276
Treatment discontinuation, <i>n</i> (%)			
Adverse events	20 (16.4%)	25 (20.7%)	0.39182
Lack of response	15 (12.3%)	50 (41.3%)	< 0.00001

($p = 0.00533$). Lack of response to therapy was observed in 50 (41.3%) patients receiving BOC and in 15 (12.3%) patients receiving TVR ($p < 0.00001$).

Treatment discontinuation due to adverse events was more prevalent in the BOC/PR group (20.6% vs. 16.4%), but the difference was not statistically significant ($p > 0.05$).

Rates of treatment responses are summarized in Table 2.

Direct costs of achieving sustained virologic response

The overall cost of BOC and TVR treatment was calculated by adding the costs of all initiated therapies. Cost of a single therapy was assessed based on its length (after adjustment to discontinuation due to adverse events or lack of response). Direct cost of achieving SVR in one patient was obtained after dividing the overall cost of treatment by the number of patients receiving SVR. The overall expenses for the treatment in 121 patients treated with BOC/PR totalled 11 418 000 Polish zloty (PLN), while the direct cost of achieving an SVR in one patient was as high as PLN 285 450. In the TVR/PR group the cost of the medications amounted to PLN 12 260 000 and achieving one SVR required PLN 185 757. Consequently, the cost of achieving an SVR in one patient with TVR therapy equalled 65% of the expenses for BOC.

Discussion

In our study an SVR was achieved in 106 out of 243 (43.6%) patients with chronic hepatitis C (genotype 1) receiving therapy based on pegylated interferon, ribavirin and BOC or TVR. The sustained virologic response rate of around 43% is much below the results reported in registration studies of both NS3/4A protease inhibitors [2-4]. It should be noted that the efficacy of BOC/TVR-based treatment is even worse than the efficacy of pegylated interferon-ribavirin therapy of 50-55% reported in other Polish studies [7, 8]. This difference may be the result of the high proportion of cirrhotic patients (138/243, 56.7%) and treatment-experienced patients (211/243, 87%) included in the study population. Such patients are at the highest risk of developing liver failure and hepatocellular carcinoma and, for that reason, had their treatment initiated as a priority. Moreover, inclusion of patients who did not respond to previous therapies was a consequence of the National Therapeutic Programme for Hepatitis C eligibility criteria, according to which NS3/4A protease inhibitor-based therapy was dedicated mainly to treat-

ment-experienced patients. Other restrictions such as inclusion of patients with severe fibrosis or patients with interleukin 28B TT subtype (a negative predictor of virologic response) may have also contributed to the low SVR rates and exceptionally high costs of the treatment. Similarly poor efficacy in study groups with high rates of treatment-experienced patients and patients with liver cirrhosis was reported by Sethi *et al.* [9] (48.5%) and Bichoupan *et al.* [10] (44%).

It is worth noting that the SVR rate in patients treated with TVR was significantly higher than in patients treated with BOC (54.1% vs. 33.1%; $p = 0.00094$). The two groups did not differ significantly in terms of age, sex, liver fibrosis and history of previous treatment. Although both drugs are members of the same class of antiviral agents – known as first generation NS3/4A protease inhibitors – their efficacy in a real life population varies and reflects the actual potential of each active substance. This observation was first reported in the Cupic study [5], where SVR rates in treatment-experienced, cirrhotic patients treated with BOC were lower than in patients treated with TVR. In a study by Salmeron *et al.* the rate of SVR by intention-to-treat analysis was also greater in patients treated with TVR (65%) than in patients treated with BOC (52%, $p < 0.0001$); however, in modified intention to treat analysis the observation was not statistically significant [11]. Differences in SVR rates between TVR and BOC have also been noted by other authors: 53% vs. 40% [12] and 56% vs. 53%, respectively [13]. None of the studies published reported an advantage of BOC.

Similar rates of TVR efficacy were observed in another Polish “real life” study investigating safety and efficacy of triple therapy with TVR in treatment-experienced patients with advanced liver fibrosis [14]. The overall SVR24 rate in this analysis was 56% and was lower in cirrhotic patients than in patients with bridging fibrosis. These observations are consistent with the results of our study.

Rates of lack of response seem to confirm significant differences in antiviral potential of the two drugs. Non-responders to BOC or TVR constituted 41.3% and 12.3% of the total, respectively ($p = 0.0001$). This clear difference may be suggestive of low ability of BOC to reduce viral load, even when administered after a 4-week lead-in of pegylated interferon and ribavirin.

At the time of our study it was believed that TVR posed a higher risk of severe adverse events. Moreover, tolerance of TVR-based therapies was also expected to be worse. Our retrospective analysis of both NS3/4A protease inhibitors in comparable groups of patients proves that rates of treatment discontinuation due to adverse events, although not significantly different,

were even higher in patients treated with BOC (20.7% vs. 16.4%, $p > 0.05$). Another Polish study yielded a similar rate of serious adverse events caused by TVR (15%) [14].

The different SVR rates for TVR and BOC observed in our study resulted in diversification of direct costs of each drug. Achieving an SVR in one patient cost PLN 285 450 if treated with BOC and PLN 185 757 if treated with TVR. This observation is in accordance with results obtained by other researchers, who also reported that treatment with TVR is less expensive and therefore more effective than treatment with BOC [15, 16]. Only Giménez-Manzorro *et al.* did not observe any significant difference in costs of the two drugs [17].

Therefore, the very high costs of antiviral agents used in the years 2013-2015 seem not to entail satisfactory therapeutic effects. However, in more detailed analyses that included the economic setting of European countries, the USA or Singapore, several authors proved that therapies based on first generation protease inhibitors were still cost-effective [10, 15, 16, 18, 19].

Conclusions

The results of our study prove that treatment with first generation NS3/4A protease inhibitors administered within the National Therapeutic Programme for Hepatitis yielded lower SVR rates and significantly higher costs than reported in their registration trials. The very low treatment efficacy may be the result of inclusion criteria that allowed treatment of patients with negative prognostic factors, such as advanced liver fibrosis/liver cirrhosis or previous treatment failure. Out of the two first generation NS3/4A protease inhibitors, TVR seems to be significantly more potent against hepatitis C virus, with similar safety and tolerance.

Disclosure

Authors report no conflict of interest.

References

- Halota W, Flisiak R, Boroń-Kaczmarek A, et al. Recommendations for the treatment of hepatitis C issued by the Polish Group of HCV Experts – 2016. *Clin Exp Hepatol* 2016; 2: 27-33.
- McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; 360: 1827-1838.
- Hézode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; 360: 1839-1850.
- Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2010; 376: 705-716.
- Hézode C, Fontaine H, Dorival C, et al. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. *Gastroenterology* 2014; 147: 132-142.e4.
- Castera L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; 128: 343-350.
- Juszczak J, Baka-Cwierz B, Beniowski M, et al. Pegylated interferon-alfa 2a with ribavirin in chronic viral hepatitis C (final report). *Przegl Epidemiol* 2005; 59: 651-660.
- Piekarska A, Zbońska J, Wójcik K, et al. The efficacy of various combinations of antiviral drugs in retherapy of chronic hepatitis C patients. *Exp Clin Hepatol* 2006; 2: 41-45.
- Sethi N, Tapper EB, Vong A, et al. Direct costs of first-generation protease inhibitors for the treatment of genotype 1 chronic hepatitis C viral infection. *J Viral Hepat* 2015; 22: 974-976.
- Bichoupan K, Martel-Laferrriere V, Sachs D, et al. Costs of telaprevir-based triple therapy for hepatitis C: \$189,000 per sustained virological response. *Hepatology* 2014; 60: 1187-1195.
- Salmerón J, Vinaixa C, Berenguer R, et al. Effectiveness and safety of first-generation protease inhibitors in clinical practice: Hepatitis C virus patients with advanced fibrosis. *World J Gastroenterol* 2015; 21: 9163-9174.
- Vo KP, Vutien P, Akiyama MJ, et al. Poor Sustained Virological Response in a Multicenter Real-Life Cohort of Chronic Hepatitis C Patients Treated with Pegylated Interferon and Ribavirin plus Telaprevir or Boceprevir. *Dig Dis Sci* 2015; 60: 1045-1051.
- Price JC, Murphy RC, Shvachko VA, et al. Effectiveness of telaprevir and boceprevir triple therapy for patients with hepatitis C virus infection in a large integrated care setting. *Dig Dis Sci* 2014; 59: 3043-3052.
- Janczewska E, Flisiak R, Zarebska-Michaluk D, et al. Effect of Peginterferon or Ribavirin Dosing on Efficacy of Therapy With Telaprevir in Treatment-Experienced Patients With Chronic Hepatitis C and Advanced Liver Fibrosis: A Multicenter Cohort Study. *Medicine (Baltimore)* 2015; 94: e1411.
- Camma C, Petta S, Cabibbo G, et al. Cost-effectiveness of boceprevir or telaprevir for previously treated patients with genotype 1 chronic hepatitis C. *J Hepatol* 2013; 59: 658-666.
- Cortesi PA, Ciaccio A, Rota M, et al. Management of treatment-naïve chronic hepatitis C genotype 1 patients: a cost-effectiveness analysis of treatment options. *J Viral Hepat* 2015; 22: 175-183.
- Giménez-Manzorro Á, García-González X, Rodríguez-González CG, et al. Cost-effectiveness and safety of telaprevir and boceprevir for chronic hepatitis C in real-world clinical practice. *Gastroenterol Hepatol* 2015; 38: 575-582.
- Dan YY, Ferrante SA, Elbasha EH, et al. Cost-effectiveness of boceprevir co-administration versus pegylated interferon- α 2b and ribavirin only for patients with hepatitis C genotype 1 in Singapore. *Antivir Ther* 2015; 20: 209-216.
- Athanasakis K, Ferrante SA, Kyriopoulos II, et al. Boceprevir for Chronic Genotype 1 Hepatitis C Virus in the Current Health Care Setting in Greece: A Cost-effectiveness Analysis. *Clin Ther* 2015; 37: 1529-1540.