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# A Real Life Boceprevir Use in Treatment-Experienced HCV Genotype 1 Patients with Advanced Fibrosis

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## ABSTRACT

**Background**: A number of high quality randomized clinical trials examining the efficacy and safety of triple therapy in genotype-1 HCV-infected patients have been published. However, these trials included a small number of patients with advanced fibrosis, and selected a population different from that in real-world settings.
**Aim**: To determine the efficacy of boceprevir, pegInterferon and ribavirin regimen in genotype-1 treatment-experienced HCV-infected patients with cirrhosis and bridging fibrosis in real-life setting.
**Method**: 167 treatment-experienced patients (85.6% relapsers) out of which 33.5% had cirrhosis, with a mean age of 52.6 years, registered in the Romanian Name Patient Program Database were included into the study.
**Results**: 16.7% of patients had a viral load >100 IU/mL. Undetectable HCV RNA was encountered in 77.3% of patients at week 12. Multiple logistic regression analysis revealed the following independent predictors, measured at week 8, for an HCV RNA ≥100 IU/mL at week 12 of triple therapy: alanine aminotransferase values (p=0.01), hemoglobin level (p=0.04) and <2log drop of viral load (p<0.0001). A stopping score at 8 weeks was created as the sum of these 3 parameters, with a total of 4 possible points. AUROC of this score was 0.84, with a sensitivity of 75% and a specificity of 86.2%.
**Conclusion**: Triple therapy in this cohort of real-life genotype-1 HCV-infected patients with advanced fibrosis showed robust early virological response (EVR) rates. A week 8 model predicting lack of EVR was created, with good clinical utility that can be validated in prospective larger cohorts.

**Key words:** chronic hepatitis C – boceprevir – advanced fibrosis.

## INTRODUCTION

Triple therapy with either boceprevir (BOC) or telaprevir in combination with pegylated interferon alpha and ribavirin has given clinicians a more effective armamentarium and has established a new standard of care for the treatment of genotype 1 chronic hepatitis C. Two large trials SPRINT-2 (including naïve patients) and RESPOND-2 (including previous treatment failure patients) have demonstrated that the rate of sustained virological response (SVR) was significantly improved with BOC plus peginterferon–ribavirin (PegIFN/RBV) compared to PegIFN/RBV alone [1, 2]. Patients who relapsed after receiving double antiviral therapy have achieved a SVR rate of up to 75%, with rates of 40 to 52% in the subgroup of patients with a previous nonresponse [2]. Bruno et al [3] showed that BOC improves SVR rates up to 82% even in patients with cirrhosis/bridging fibrosis treated for 48 weeks (full-duration and not response guided therapy) in the two above mentioned phase 3 trials. Predictors of SVR included previous relapse (vs previous partial response) [2], low baseline viral load ≤800,000 IU/mL [2], absence of cirrhosis [1, 2] and a response at week 4 [1, 2]. The 4-week lead-in decrease of viral load less than 1 log defines patients in whom the addition of BOC results in low SVR rates (≈35%). However, this criterion was not established as a predictor for non-response at week 12 during triple therapy. Moreover, patients with HCV genotype 1b treated with BOC had higher SVR rates compared to genotype 1a (66-73% vs 53-64%) [4]; this is a good reason to use protease inhibitor based treatment in Romanian chronic hepatitis C patients where genotype 1b HCV exceeds 99% [5].

According to current estimates based on the recently published population-based epidemiological study [6], the prevalence of 3.23% of HCV infection in the general population in Romania represents one of the highest figures in Europe. In a previously published paper [7], we stated that only 25,318 patients with chronic hepatitis C were treated during 2002-2009, corresponding to a cumulative proportion of 4.1% of the prevalent cases of HCV infection treated in Romania until 1st of January 2010. In addition, the consequences of HCV infection in terms of chronic hepatitis C with advanced fibrosis or cirrhosis will continue to evolve until 2030 (prevalence of HCV-related liver cirrhosis and hepatocellular carcinoma will continue to increase in Romania from 88,124 and 1,708 cases in 2009 to 146,209 and 2,686 cases, respectively, in 2030) [8]. In these patients, successful antiviral therapy is warranted in order to stop the progression of disease to decompensated cirrhosis and hepatocellular carcinoma and implicitly to decrease the subsequent costs associated with the management of these complications and reduce the need for liver transplantation.

The Romanian Name Patient Program (NPP), taking into consideration the above mentioned facts was started in patients with F3/F4 METAVIR stages with the highest need to be cured.

The aim of this multicenter, prospective study was to evaluate the efficacy and safety of BOC-based triple therapy in treatment experienced patients with chronic hepatitis C and advanced fibrosis in daily practice; a second aim was to establish baseline and on-treatment predictors of the presence of HCV RNA >100 IU/mL at 12 weeks during triple therapy.

## PATIENTS AND METHOD

### Patient's selection

Adult (18-65 years old), treatment experienced genotype 1 HCV infected patients with histologically advanced hepatitis C (F3-F4 stages using METAVIR assessment) on liver biopsy performed within 24 months prior to the enrollment or non-invasive fibrosis evaluation by Fibroscan (Echosens) or Fibrotest (Biopredictive) within 3 months prior to the enrollment were prospectively included in the study in 8 Romanian Gastroenterology/Infectious Diseases Centers. Plasma HCV RNA levels were measured using the TaqMan 2.0 assay (Roche Diagnostics), which has lower limits of quantification and detection of 25 and 9.3 IU/mL, respectively; the lower limit of detection was used for decision making at various points throughout the study. Study enrollment began in September 2011 and lasted until August 2013. That is the reason why only predictors for 12 weeks on treatment viral load value were evaluated and reported; results for SVR are not available yet for all 241 included patients.

Patients were excluded due to one or more of the following: HCV RNA ≤10,000 IU/mL; white blood count <3,000/mm$^3$; neutrophils <1,500/mm$^3$; platelet count <80,000/mm$^3$; hemoglobin level lower than 12 g/dL for females and 13 g/dL for males; HBV/HIV coinfection; other coexistent liver disease identified by appropriate serology, genetic testing, or histologic assessment; organ recipients including patients with recurrent hepatitis C after liver transplantation; ongoing regular alcohol consumption exceeding 20 g/day for women and 30 g/day for men or active use of illicit drugs; antecedent/ concurrent severe psychiatric illness; uncontrolled thyroid dysfunction; clinically significant pulmonary, renal, cardiac or cardiovascular disease; clinically significant bleeding disorders; poorly controlled diabetes; current pregnancy and lactation; unable/unwilling to use contraception during the treatment and 6 months after discontinuation.

Written informed consent was obtained before the initiation of the therapy. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the local Ethical Committees of the host institutions.

### Exposure to therapy and follow-up

Eligible patients received therapy with PegInterferon (Peg-IFN) α-2b (Peg-Intron®, Schering Corporation, MERCK & CO., INC., Whitehouse Station, NJ 08889, USA) 1.5 μg/kg once per week subcutaneously (<60 kg 80 μg/week; 61-75 kg 100 μg/week; 76-85 kg 120 μg/week; >85 kg150 μg/week) plus ribavirin (RBV) (Rebetol®, Schering Corporation, MERCK & CO., INC., Whitehouse Station, NJ 08889, USA) 800-1400 mg/day orally, according to body weight (<65 kg, 800 mg/day; 65-85 kg 1000 mg/day; >85 to 105 kg, 1200 mg/day; >105 kg 1400 mg/day).

Boceprevir (Victrelis®, Merck Sharp & Dohme Corp., MERCK & CO., INC., Whitehouse Station, NJ 08889, USA) was administered orally at a dose of 800 mg three times daily (to be taken with food and with an interval of 7-9 hours between doses) in four capsules of 200 mg each.

All patients received PegIFN/RBV during the 4-week lead-in period, followed by oral BOC for 44 weeks. The stopping rules were applied as follows: therapy was discontinued in patients whose HCV RNA levels were > 100 IU/mL at treatment week 12, as well as in those who had detectable HCV RNA at any time between weeks 24 to 48. Patients enrolled in the study were prospectively evaluated as outpatients by the study staff at baseline, 4, 8, 12, 24, 36 and 48 weeks of therapy, at 12 and 24 weeks post-treatment.

A flow chart was established in the database for each patient, recording clinical changes, serial laboratory results, side effects, dose modifications and decision/reasons for treatment discontinuation. A liberal approach was used for dose adjustment in order to maintain hemoglobin (Hb) level >8 g/dL, absolute neutrophil count >750/mm$^3$ and thrombocytes >75,000/mm$^3$, taking into account the current recommendations on the package insert for the PegIFN, RBV and BOC. RBV dose reduction was recommended when the Hb level was <10 g/dL and RBV interruption was recommended when Hb level was <8.5 g/dL. At the discretion of the study investigator, RBV could be increased to full dose directly or in steps, respectively, when the adverse event subsided. The use of erythropoietin (EPO) was indicated in case of Hb levels <9.5g/dL despite RBV reduction by 25-50%. Blood transfusion was indicated when Hb level decreased <8.5g/dL.

### Statistical analysis

Continuous variables are presented as mean and standard deviation, while categorical variables are reported as frequencies and percentages. Univariate comparisons between quantitative variables were performed using the Wilcoxon rank sum test, and between categorical variables using chi squared test. We tested separately the association between clinical or

biochemical parameters and lack of early virological response (EVR) (defined as HCV RNA ≥100 IU/mL at 12 weeks) using logistic regression. Crude odds ratios (ORs) were calculated with the corresponding 95% confidence intervals (CIs). The diagnostic performance of each clinical or biological parameter (independent variables) to discriminate the absence of EVR was evaluated through receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) with the corresponding sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated. The cut-off values were selected from the receiver operating characteristic (ROC) curve to maximize the total sensitivity and specificity.

All statistical tests were two-sided and a level of $P < 0.05$ was used to indicate statistical significance. All statistical analyses were carried out using SPSS statistics 15.0 (SPSS Inc, Chicago, IL, USA).

## RESULTS

### Patients' characteristics

One hundred and sixty seven treatment experienced patients (85.6% relapsers, 7.2% null-responders and 7.2% partial responders) with bridging fibrosis (66.5% F3 METAVIR) or cirrhosis (33.5% F4 METAVIR), registered in the Romanian NPP database were included into the study and followed prospectively. There were 52.7% males with a mean age of 52.6 ± 11.3 years and a mean weight of 81.6 ± 15.4 kg. Only 22.2% of the patients had a previous antiviral double therapy with Peg-IFNα-2b, the rest (77.8%) had undergone a Peg-IFNα-2a treatment regimen. Median baseline viral load was 1,228,576 (104,734 – 55,485,305) IU/mL and a high HCV RNA > 800,000 IU/mL was present in 55.6% of patients. At baseline, significant differences were observed between patients with cirrhosis and patients with bridging fibrosis regarding weight, ALT, thrombocytes, but not for age, Hb, leucocytes and viral load (Table I).

### Predictors of HCV RNA >100 IU/mL at week 12

In this real-life study, after the lead-in period, 19.7% (33) of patients had a more than 2log decrease in viral load compared to baseline and 29.3% (49) had a less than 1 log reduction in HCV RNA; 61.6% (103) of patients had > 2log decrease in HCV RNA compared to baseline after 4 weeks of BOC and respectively, 8 weeks of therapy. At week 12, 16.7% (28) of patients had a viral load >100IU/mL; undetectable HCV RNA was encountered in 77.3% (129) of patients.

**Table I**. Patients' characteristics (mean ± SD) according to the fibrosis stage at baseline

| Variable | F3 METAVIR | F4 METAVIR | p value |
|---|---|---|---|
| Age (years) | 52.5 ± 9.5 | 54.1 ± 8.4 | 0.30 |
| Weight (kg) | 80.5 ± 13.7 | 85.3 ± 14.4 | 0.03 |
| ALT (IU/L) | 80.3 ± 50.2 | 107.6 ± 83.3 | 0.03 |
| Hb (g/dL) | 14.6 ± 1.2 | 14.5 ± 2.4 | 0.88 |
| Leucocytes/ $mm^3$ | 6104.1 ± 1596.8 | 6379.8 ± 2100.4 | 0.42 |
| Thrombocytes/ $mm^3$ | 210292.8 ± 57449.2 | 183214.3 ± 56385.2 | 0.004 |
| Viral load (IU/mL) | 3,487,912.5 ± 523,821.6 | 2,996,183.2 ± 1,015,160.1 | 0.66 |

Logistic regression analysis showed a statistically significant positive association of baseline ALT, ALT value and Hb level at 8 weeks during therapy, presence of cirrhosis with presence of a viral load >100 IU/mL at week 12. We found that the risk of lack of virological response at 12 weeks during antiviral triple therapy increased with increasing baseline and week 8 ALT values, as well as with higher Hb levels at week 8. On the other hand, a decrease of <1 log of HCV RNA at week 4 of therapy and a decrease of <2 log at week 8 was negatively associated with virological response at week 12 (Table II). Multiple logistic regression analysis revealed the following independent predictors measured at week 8 for an HCV RNA ≥100 IU/mL at week 12 of triple therapy: ALT value (p=0.01), Hb level (p=0.04) and < 2 log drop of viral load (p<0.0001).

**Table II**. Association between clinical/biological parameters and presence of a viral load >100 IU/mL at week 12

| Variable | OR | 95% CI for OR | P value |
|---|---|---|---|
| Baseline ALT (IU/L) | 1.0116 | 1.0053 to 1.0180 | 0.0003 |
| F4 METAVIR | 2.4103 | 1.0515 to 5.5251 | 0.03 |
| Hb level at 8 week (g/dL) | 1.6357 | 1.2772 to 2.0948 | 0.0001 |
| ALT at 8 week (IU/L) | 1.0211 | 1.0089 to 1.0334 | 0.0007 |
| >1log HCV RNA decrease at week 4 | 0.1276 | 0.0407 to 0.3995 | 0.0004 |
| >2log HCV RNA decrease at week 8 | 0.0985 | 0.0383 to 0.2531 | <0.0001 |

The area under the ROC curve was calculated to establish the statistical performance of each independent predictor of non-response at 12 weeks. As an individual parameter, ALT value at week 8 presented an AUROC of 0.71 (good clinical utility for non-response prediction) with sensitivity of only 48.1%, but a specificity of 92.2% and a positive likelihood ratio (+LR) of 6.21 for a cut-off value of 55 IU/L. Hb level at week 8 with a cut-off value >11.7 g/dL showed an AUROC of 0.73, a sensitivity of 60.7%, a specificity of 80.5%, a positive predictive value (PPV) of 39.5%, but a negative predictive value (NPV) of 90.7% and a positive LR of 3.21.

Based on the identified 3 independent predictors of non-response at week 12 of therapy, we proposed a model that can predict lack of virological response and can be a useful tool to stop therapy earlier, at week 8 during triple therapy in daily practice. For ALT value >55 IU/L and Hb level >11.7g/dL, one point was assigned in the score. For < 2log decrease in HCV RNA at week 8 compared to baseline, we assigned 2 points. A stopping score at 8 weeks was created as the sum of these 3 parameters, with a total of 4 possible points. AUROC of this stopping score was 0.84, with a sensitivity of 75%, a specificity of 86.2%, a PPV of 58.3%, a NPV of 93.1% and a positive LR of 5.45 (Fig. 1). A cut-off ≥2 points has a diagnostic accuracy of 84% for predicting lack of virological response at week 12.

### Safety and tolerability of BOC-based triple therapy

Despite rather frequent side effects attributed to either Peg-IFN (42.5%), RBV (40.7%) or BOC (33.5%), only a minority of patients permanently discontinued therapy (5.4%,

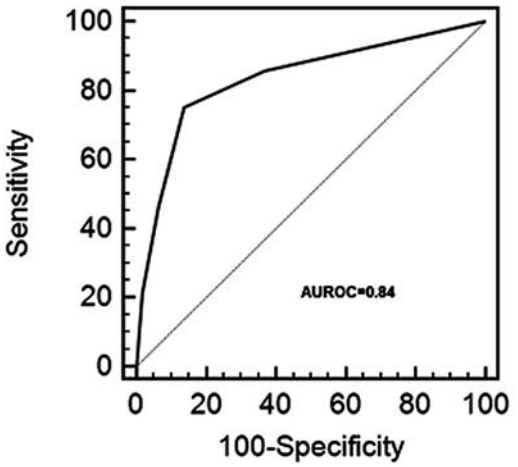


**Fig. 1.** ROC curve of biological and virological parameters model evaluated at 8 weeks which accurately predicts lack of virological response at 12 weeks during boceprevir-based triple therapy.

9 patients) due to reasons other than not fulfilling virological endpoints. The causes of treatment discontinuation were: severe psychiatric side effects (1 patient), severe hematological abnormalities (3 patients), occurrence of severe skin rash (1 patient), and development of autoimmune hepatitis during antiviral therapy (1 patient), personal reasons (2 patients) and one sudden death during therapy. Anemia was the most frequent side effect (45.5% of patients) out of the hematological adverse events. Anemia was classified as grade 1 in 23.9%, grade 2 in 18.5%; grade 3 (6.5-8g/dL) anemia was encountered only in 3% of patients. None of the patients had grade 4 anemia. EPO was used in 12.6% of patients, while blood transfusions were required in 17.3% of patients. Neutropenia was encountered in 34.2%, but neutrophils <750/mm$^3$ were found in 17.4% of patients. Filgastrim (G-CSF) was administered in 13.8% of patients as required due to neutropenia. In all cases the use of G-CSF allowed the maintainance of the whole dose of Peg-IFN. Side effects due to EPO were not encountered, except in one patient that had a transient, sudden increase in blood pressure after the first EPO administration; after G-CSF administration there were influenza-like symptoms in all patients. A percentage of 10.8% of patients had mild thrombocytopenia (all patients had >75,000/mm$^3$). Ribavirin dose reductions were necessary in 53.2% of patients due to anemia and fatigue. Peg-IFN was reduced in 7.2% of patients due to weight loss.

Hemoglobin, neutrophils and thrombocytes decreased throughout the study period and the decrease was statistically significant for all cell counts compared to the beginning of study. There was no statistical significant difference for Hb or neutrophils at week 4, 8 or 12 between patients with cirrhosis or bridging fibrosis. Thrombocyte counts at week 4, 8 and 12, respectively, were significantly lower in the F4 group compared to the F3 group (p=0.01; p=0.04 and p=0.03, respectively).

Dysgeusia occurred in 21.1% of patients. Fatigue was the most frequently reported side effect, in 56.9% of patients. Other adverse events were: weight loss, anorexia, nausea, headache and influenza-like in 38.3% of patients. The most frequent biochemical abnormalities were hypertriglyceridemia and hyperuricemia that occurred in 47.3% of patients.

## DISCUSSION

Clinicians face a continuous dilemma regarding "who should be treated first with the new antivirals?" The "easy to treat" patient with young age and mild fibrosis and the highest chances of SVR or patients "difficult to treat" with bridging fibrosis/cirrhosis, advanced age, null-responders, that are in the greatest need to receive these new potent drugs hoping that they will be cured?

In countries with cost constraints and limited resources, despite the increased number of patients requiring antiviral therapy, some providers may face challenging decisions on a per-patient or practice-wide basis. In such cases, probably, the patients prioritized for treatment should be the ones with the greatest need, that is, patients with advanced fibrosis or cirrhosis, with due consideration also given to the likelihood of response [9]. However, association of a protease inhibitor to Peg-IFN and RBV increased considerably the chance of cure even in this category of patients. The stage of fibrosis is still an important predictor of SVR [1]. In these difficult-to-treat patients, the addition of telaprevir for 12 weeks improved SVR rates to 62%, while the addition of BOC for 44 weeks showed SVR rates of 52% in naïve hepatitis C F3/F4 patients [10]. We also showed that treatment-experienced patients with cirrhosis had a lower chance of achieving EVR compared to bridging fibrosis. This is in contrast to the study of Bruno et al [3] that showed similar SVR rates in patients with F3 vs F4 fibrosis stage, if they have received BOC/Peg-IFN/RBV for 48 weeks. However, patients with F4 and good response to Peg-IFN after a lead-in period that received BOC according to response guided therapy had a lower SVR rate compared to patients with F3 (45% vs 62%) [3].

Interferon responsiveness, as demonstrated by the week 4 lead-in responses, was an important predictor of SVR in patients with advanced fibrosis [1, 2]. A decrease in viral load <1log at week 4 was indicative of low response during treatment at 12 weeks in our study. In SPRINT-2 and RESPOND-2 studies, SVR was more likely in patients with advanced fibrosis and undetectable HCV RNA at week 8 [1, 2]. Our results showed that a decrease >2log in viral load at week 8 was an independent predictor of a 12 week virological response and this should motivate clinicians and patients to continue therapy.

The development of anemia, defined as hemoglobin level <10g/dL during treatment is associated with higher SVR rates in double antiviral therapy [11, 12]. However, in the telaprevir-containing regimens, SVR rates were preserved in patients, whether Hb level fell <10g/dL or not (74% vs 73%) [13]. In contrast, in the BOC-based regimen, reduction to Hb <10g/dL led to a SVR of 72% vs 58% in those who did not achieve anemia [14]. This is in accordance to our results, showing that anemia after 4 weeks of BOC is indicative of 12 weeks on treatment virological response, and consecutively of SVR.

This is the first study that has developed a clinical, easy to use in daily practice, model of prediction of lack of virological response at week 12 of therapy, using variables from week 8. This allows an earlier stopping rule, especially in a F3-F4 population with higher reported hematological side effects that could impact morbidity and even mortality. In addition, this strategy is reasonable and should be used in countries such

as Romania with limited financial resources and where triple-based antiviral therapy is not yet implemented as a standard of care in hepatitis C patients and is not reimbursed yet by the National Health Insurance Agency. This 8 week model in BOC-treated patients proved a good clinical utility and should be tested in a prospective larger cohort of patients with previous failure of treatment.

Alanin aminotransferases at week 8 of therapy are also for the first time mentioned as a predictor of non-response. This may be linked indirectly to the higher necroinflammatory activity. A limitation of the study is that activity on the METAVIR score was not assessed as a separate factor, because not all patients had liver biopsy in the era of non-invasive markers for fibrosis evaluation.

Another limitation of our study is the lack of the analysis of IL28B genotypes as a predictor of virological response, but it has been shown to be of limited value in previously experienced patients. In patients with IL28B CT and TT genotype, the addition of telaprevir or BOC to Peg-IFN and ribavirin significantly improved SVR; while the presence of IL28B CC genotype appears to be predictive for a short duration of therapy [15, 16]. However, we can suppose, as demonstrated in our transplanted population [17], that the majority of patients were IL28B genotype CT/TT and also this study population is probably non-CC genotype. Thus, in this situation, IL28B is probably not important for on treatment virological response.

BOC-based regimen in previously treated patients with advanced fibrosis in daily practice is safe. Anemia is encountered in a proportion similar to other non-real life studies [18, 19]. A difference is in the management of anemia; apart from RBV dose reductions, EPO was used in only 12.6% of patients in our study, similar to the IDEAL study where 16.3% of patients received EPO [20]. In contrast, in a study recently published of HCV treatment-naïve patients, 43% of all patients receiving BOC/Peg-IFN/RBV and 78% of those who became anemic on this regimen were treated with adjuvant EPO [14]. Our study had the highest reported frequency (17.3%) for blood transfusions in order to maintain Hb level over 8.5g/dl. In the CUPIC study, cirrhotic patients treated with telaprevir-based regimen required transfusions in 16% of cases, while only 6% of BOC-based treated patients received packed red cell transfusions [21]. The reason for the higher use of blood transfusion and lower EPO use in our country is the fact that EPO is not reimbursed by the Health Insurance Agency and costs supported by the patient are very high. Anemia is one of RBV major toxicity outcomes. There are studies [22, 23] that mention RBV plasma concentration monitoring as a tool for optimizing anti-HCV therapy in patients with expected poor tolerability. However, anemia can be used as an indirect indication that RBV levels are therapeutic even at higher levels, thus causing hematological toxicity despite RBV dose changes.

## CONCLUSION

We propose an 8 week clinical model of prediction for stopping therapy in BOC-based regimens used in patients with advanced fibrosis. Such a strategy would minimize costs and prevent an alteration of the quality of life due to adverse events. Validation of this score should be performed in prospective studies. Real-life triple therapy is highly efficacious and safe and should be used as a standard of care also in Romania. An SVR after antiviral therapy leads to improved clinical outcomes mainly in patients with advanced fibrosis.

**Conflicts of interest:** No funding was received for this study. Liana Gheorghe is speaker and served on the advisory board for Merck Sharp&Dohme, Janssen-Cilag, Hoffman-La Roche, Bristol-Myers Squibb, Gilead and Abbott; Speranta Iacob and Iulia Simionov have served as speakers for Merck Sharp&Dohme; Florin Caruntu is speaker and served on the advisory board for Hoffman-La Roche, Bristol-Myers Squibb, Merck Sharp&Dohme, Gilead, Janssen-Cilag, Abbott and GlaxoSmithKline; Adriana Motoc, Victoria Arama, Liliana Preotescu, Ion Stefan, Adrian Goldis, Cristian Brisc, Sorin Rugina, Nicolae Rednic have no conflicts to declare.

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