BLEEDING EVENTS IN PATIENTS WITH HCV- RELATED LIVER CIRRHOSIS TREATED WITH DIRECT ACTING ANTIVIRALS - FACT OR NATURAL COURSE ?

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BLEEDING EVENTS IN PATIENTS WITH HCV- RELATED LIVER CIRRHOSIS TREATED WITH DIRECT ACTING ANTIVIRALS-FACT OR NATURAL COURSE ? (Abstract) **Aim**: We aimed to assess the incidence and risk factors of bleeding events in cirrhotic patients with sustained virological response (SVR) treated with direct-acting antivirals (DAAs) therapy. **Material and methods:** We retrospectively analyzed a cohort of patients with HCV-related liver cirrhosis treated with paritaprevir/ritonavir, ombitasvir and dasabuvir(PrOD) ± ribavirin and ledipasvir/sofosbuvir (LED/SOF) ± ribavirin for 12/24 weeks, in a tertiary gastroenterology referral center from North-Eastern Romania, between January 1st2016 and January 1st, 2019. All patients with presumption of digestive bleeding (hematemesis or melena) were evaluated and confirmed by upper digestive endoscopy. Patients known with thrombophilia were not included in the study group. **Results:** The study included 874HCV-infected cirrhotic patients treated with PrOD or LED/SOF ± RBV, with documented SVR, mean age 58,7±6,2years, predominantly female (58%). Of the total number, 443 (50.68%) received PrOD and 431 (49.31%) patients were treated with LED/SOF ± RBV. From all, 572 (65.34%) patients had Child-Pugh class A, 226 (25.96%) class B and 76 (8.7%) class C cirrhosis. Mean period from SVR and the occurrence of bleeding events was 230±121 days. Bleeding complications after SVR were reported in 16(1.83%) patients: 9 (56.25%) with variceal hemorrhage and7 (43.75%) with non-variceal hemorrhage. There was no significant change in prothrombin serum levels (baseline values in patients treated with PrOD was 11.67 ± 0.91 versus 11.70 ± 0.83 at SVR, p=0.993, respectively 11.5 ± 0.84 sec at baseline versus 11.4 ± 0.68 at SVR, p=0.715 in patients treated with LED/SOF+RBV) and platelet count (126 000 (101 500-162 000)*vs*. 131 000 (101 000-165 000), p=0.818 in patients treated with PrOD, respectively 94857.14±32 *vs*. 92428.57 ± 35, p= 0.853, in patients treated with LED/SOF+RBV).**Conclusions**: Bleeding events in patients with HCV-related liver cirrhosis treated with DAAs are not influenced by the variations of coagulation parameters, rather correspond to the hemodynamic changes induced by the status of advanced liver disease. It should be underlined that the bleeding events were mostly variceal bleeding, due to persistent portal hypertension despite viral eradication. **Keywords**: DIRECT ACTING ANTIVIRAL THERAPY, SUSTAINED VIROLOGIC RESPONSE, BLEEDING COMPLICATIONS, LIVER CIRRHOSIS.

The complications of liver cirrhosis frequently occur in the evolution of the disease, with a negative impact on the prognosis of patients.

In daily practice, we frequently meet cirrhotic patients who associate bleeding complications, especially variceal bleeding sustained biologically by prolonged bleeding and coagulation times, which is why it was assumed that these patients are characterized by a state of hypocoagulability induced by the deficiency of coagulation factors (1, 2).

Although thrombotic events may occur in the development of liver cirrhosis, bleeding is much more frequent and is based on a complex mechanism that involves increased pressure in the portal system, changes in vascular endothelium and coagulation disorders (3).

The vascular endothelium plays a central role in the pathophysiology of portal hypertension and in the control of coagulation. Physiologically the hepatic sinusoidal endothelial cells are different from the rest of the endothelial cells in the body because they have fenestrations, do not have platelet adhesion molecules (PECAM1 or CD31), E-selectin, and have no basement membrane. Capillary hepatic sinusoids determine their transformation into vascular endothelial cells with loss of fenestration, basal membrane formation, and expression of new surface adhesion molecules. All these changes contribute to an increased resistance to flow and the development of portal hypertension in cirrhotic patients (4).

The bleeding complications encountered in cirrhotic patients may be due to portal hypertension (bleeding from the esophageal, gastric, ectopic varices, portal gastropathy) or, in the advanced stages of the disease, by the status of hypocoagulability that could be associated with the appearance of cutaneous, mucosal or intracranial bleeding(5).

Portal pressure, assessed by hepatic venous pressure gradient (HVPG) measurement, determines the development of liver-related complications and mortality in patients advanced chronic liver disease. Variceal bleeding is one of the most severe complications associated with liver cirrhosis, being the most significant complication of portal hypertension, which is associated with a high early mortality (20% at 6 week)(6).

Since the onset of esophageal varices, the risk of bleeding is mainly related to local hemodynamic factors and mechanical parameters such as the pressure gradient between the hepatic vein and the portal vein, the degree of varicose veins, the presence of *cherry spots* and the severity of liver cirrhosis (7).

Direct-acting antivirals (DAAs) have radically changed the management of chronic HCV infection over the past years through high effectiveness and safeness, with a major impact on the prognosis and burden of the disease. The DAAs mechanism of action directly targets viral protease, polymerase and nonstructural proteins, thus allowing a high rate of viral clearance without significant side effects (8).

Sustained virologic response (SVR) is now achieved in >90% of the patients and is associated with improvements in liver function, fibrosis and overall survival. Portal hypertension is also expected to improve with virological response, along with the improvements in liver inflammation and liver fibrosis (9). The knowledge of the effects of hepatitis C virus (HCV) elimination on clinically significant outcomes like portal hypertension and its

complications is thus of unremarkable importance since it can influence management after SVR (10).

Recent studies have shown the positive impact on liver function, as measured by the CHILD-PUGH and MELD score, as well as the decompensation rate after obtaining SVR with the new oral direct-acting antivirals, but there are no conclusive data regarding the effect on clotting disorders due to liver cirrhosis (11). In our study, we aimed to assess the incidence and risk factors of bleeding events in cirrhotic patients with SVR treated with DAAs therapy.

MATERIALS AND METHODS

This is a retrospective study in which we included patients with HCV-related liver cirrhosis which fulfilled the criteria for antiviral therapy, conducted in a tertiary gastroenterology referral center from North-Eastern Romania, between January 1st, 2016 and January 1st 2019. The inclusion and exclusion criteria was according to our National Protocol. The regimens used were: Paritaprevir/Ritonavir, Ombitasvir and Dasabuvir (PrOD) ± Ribavirin in patients with HCV-related compensated liver cirrhosis (LC) and Ledipasvir/Sofosbuvir (LED/SOF)+Ribavirin (RBV) for 12/24weeks, in patients with compensated and decompensated LC. Diagnosis of cirrhosis was established based on clinical features, blood tests and imaging methods.

The study protocol was approved by the Ethical Research Committee of "Grigore T. Popa" University of Medicine and Pharmacy Iasi and by the Ethical Committee of the "Sf. Spiridon" County Clinical Emergency Hospital. All patients were required to sign an informed consent.

The diagnosis of liver cirrhosis was established by abdominal ultrasound (Philips HD 11xe ultrasound system) and non-invasive techniques for assessing liver fibrosis (Fibroscan and Fibromax). Blood tests were performed at baseline,at12/24 weeks after end of treatment (sustained virological response- SVR12) and during the presentation for digestive bleeding. All patients with presumption of digestive bleeding (hematemesis or melena) were evaluated and confirmed by upper digestive endoscopy performed in emergency and blood samples.

Statistical analysis. Data collected was statistically analyzed using *SPSS 20.0* (Chicago, IL, SUA). tests were two-tailed with p-value <0.05 was considered statistically significant. The quantitative variables were compared using the t-Student test, and the qualitative parameters were evaluated by the chi-square test.

RESULTS

The study included 874 HCV-infected cirrhotic patients treated with PrOD or LED/SOF± RBV, between January 1st, 2016 and January 1st, 2019, with documented SVR, mean age58,7 ± 6,2 years, predominantly female (58%). Of the total number, 443 (50.68%) received PrOD and 431 (49.31%) patients were treated with LED/SOF ± RBV. From all, 721 (82.49%) had compensated LC and 153 (17.50%) had decompensated LC. Child-Pugh score at baseline was 8.64 ± 1 in the LED/SOF ± RBV group versus 5.06±0.24 points (tab. I).

All patients had SVR documented by undetectable HCV-RNA. In patients treated with PrOD, GGT, AST and ALT had significant decreased values at SVR12 compared to baseline (p<0.001). Also, in the LED/SOF±RBV group, transaminases levels had an improving trend (p<0.001) (tab II, III).

TABLE I

Demographic characteristics at baseline

Demographic characteristics at baseline	All (n=874)
Females, n (%)	507 (58%)
Age (mean ± SD)	58,7 ± 6,2
Treatment Regimen	
PrOD, n (%)	443 (50.68%)
LED/SOF+RBV, n (%)	431 (49.31%)
CHILD-PUGH Score	
PrOD (mean ± SD)	5.06 ± 0.24
LED/SOF±RBV (mean ± SD)	8.64 ± 1
Stage of liver disease	
Compensated LC	721 (82.49%)
Decompensated LC	153 (17.50%)
Demographic characteristics at baseline	**All (n=874)**
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Stage of liver disease	
Compensated LC	721 (82.49%)
Decompensated LC	153 (17.50%)

TABLE II

Dynamic of biochemical parameters in patients treated with PrOD at baseline *vs.* SVR12

Parameters	Baseline	SVR12	p
PLT (/mm^3), median (IQR)	126 000 (101 500-162 000)	131 000(101 000-165 000)	0.818
INR, median (IQR)	1.1 (1.06-1.2)	1.19 (1.12-1.21)	0.002
TP (sec)	11.67 ± 0.91	11.70 ± 0.83	0.993
AST (U/L), median (IQR)	80 (55.5-120)	24 (21-32)	<0.001
ALT (U/L), median (IQR)	85 (62-119.5)	23 (20-33)	<0.001
GGT (U/L), median (IQR)	66 (40-108)	35 (23-55)	<0.001
Bilirubin (mg/dL), median (IQR)	0.93(0.77-1.38)	0.89 (0.61-1.1)	0.038
Creatinine (mg/dL) (mean ± SD)	0.76 ± 0.1	0.83 ± 1.67	0.004
Hb (g/dL)	14.27 ± 1.54	13.48 ± 1.59	0.002
Albumin (g/dL)	4.06 ± 0.43	4.01 ± 0.29	0.557
MELD	7.8 ± 1.79	7.39 ± 1.82	0.192

TABLE III

Dynamic of biochemical parameters in patients treated with LED/SOF at baseline *vs.* SVR12

Parameters	Baseline	SVR12	P
PLT (mm^3), (mean ± SD)	94857.14 ± 32	92428.57 ± 35	0.853
INR, (mean ± SD)	1.28 ± 0.12	1.20 ± 0.08	0.05
TP (mean ± SD)	11.5 ± 0.84	11.4 ± 0.68	0.715
ALT (U/L), (mean ± SD)	86 ± 49.72	24.07 ± 13.33	< 0.001
AST (U/L), (mean ± SD)	76 ± 32.45	25 ± 18.29	< 0.001
GGT (U/L), (mean ± SD)	43.64 ± 19.66	33.71 ± 15.34	0.148
BT (MG/dL), (mean ± SD)	2.05 ± 0.66	1.50 ± 0.71	0.044
Creatinine (mg/dL) (mean ± SD)	0.7 ± 0.22	0.73 ± 0.15	0.626
Hb (g/dL), (mean ± SD)	12.82 ± 1.51	13.17 ± 1.50	0.544
Albumin (g/L), (mean ± SD)	3.30 ± 0.52	3.71 ± 0.39	0.026
MELD (mean ± SD)	12.46 ± 3.07	9.5 ± 3.32	0.024

Mean period from SVR and the occurrence of bleeding events was 230±121 days.

Bleeding complications after SVR were reported in 16 (1.83%) patients: 9 (56.25%) with variceal hemorrhage and 7 (43.75%) with non-variceal hemorrhage (3 (18.75%)- portal hypertensive gastropathy, 2 (12.5%)- gastric ulcer,1(6.25%)- duodenal ulcer, 1 (6.25%)- Mallory-Weiss syndrome). Four patients had previous episodes of variceal hemorrhage before initiating direct antiviral therapy (fig.1).

From all patients, 572 (65.34%) patients had LC Child-Pugh class A, 226 (25.96%) class B and 76 (8.7%) class C cirrhotic patients (fig. 2).

There was no significant change in prothrombin serum levels in both groups: baseline values in patients treated with PrOD was 11.67±0.91 versus 11.70±0.83at SVR, p=0.993, respectively 11.5±0.84 sec at baseline versus 11.4±0.68 at SVR, p=0.715 in patients treated with LED/SOF + RBV (fig.3).

Platelet count had no significant changes at baseline versus SVR in both groups (126 000 (101 500-162 000) *vs*. 131 000 (101 000-165 000), p= 0.818 in patients treated with PrOD, respectively 94857.14±32 *vs*. 92428.57±35, p= 0.853, in patients treated with LED/SOF+RBV) (fig. 4).

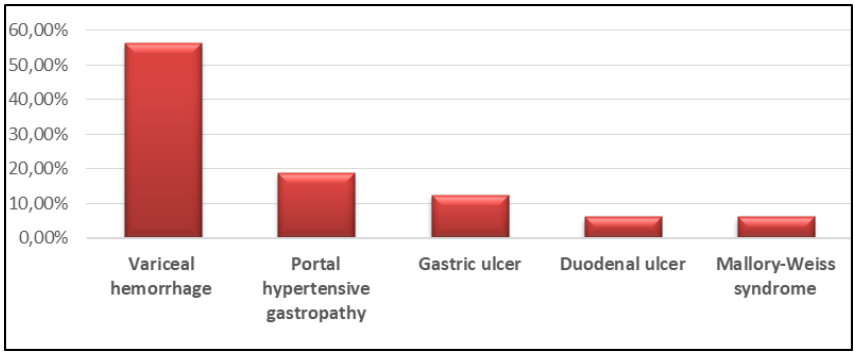

Fig. 1. Bleeding events after SVR12

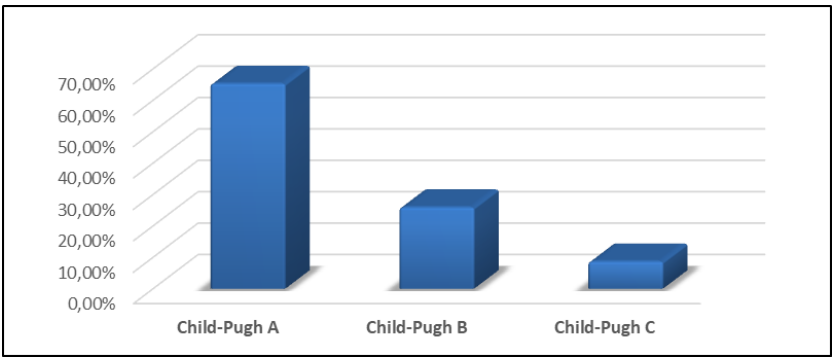

Fig. 2. Distribution of patients according to severity of liver disease evaluated with CPS

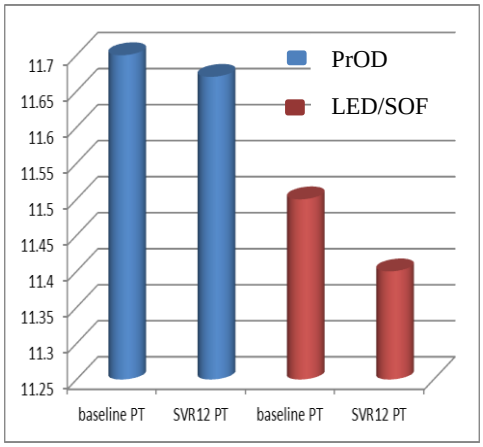

Fig. 3. Prothrombin serum levels at baseline and SVR12

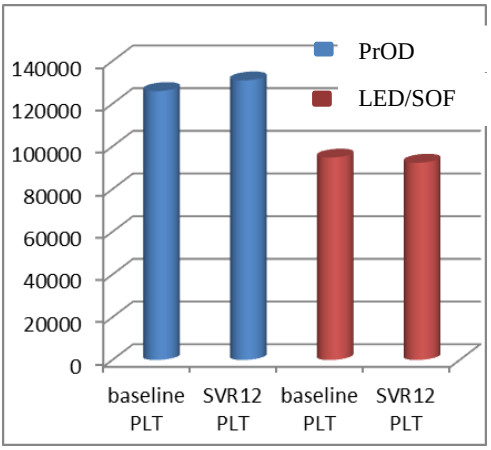

Fig. 4. Platelets count at baseline and SVR12

DISCUSSION

The last few years brought an important change in the therapeutic management of chronic HCV infection. Direct antiviral agents (DAAs) are highly effective and safe and are changing the prognosis and burden of the disease. Sustained virologic response (SVR) is now achieved in more than 90% of cases and is associated with improvements in liver function, fibrosis and overall survival (12).

In order to accomplish the goal of HCV elimination as an important health public threat by 2030, HCV treatment is nowadays recommended in almost all infected patients, even those without significant fibrosis. This, together with the high SVR rates and the safety profile of DAAs, can change the history of HCV infection and improve clinical outcomes namely by avoiding the development of portal hypertension and improving it in patients with patients with established portal hypertension (13).

Although thrombotic events may occur in the natural course of liver cirrhosis, bleeding is much more frequent in clinical practice. The available data from the last few years showed that there is an imbal-

ance concerning the hemostasis status in cirrhotic patients which are considered to be predisposed to bleeding events; many studies have demonstrated a disturbance of the balance between pro- and anticoagulants factors in cirrhotic patients. There are very few studies regarding the coagulation status of cirrhotic patients with SVR treated with DAAs (11). In our study we aimed to assess the incidence and risk factors of bleeding events in patients with SVR treated with DAAs.

Our study showed an incidence of 1.83% of bleeding events in patients with HCV related liver cirrhosis treated with DAAs.

There was a slight improvement of platelet count after SVR in patients treated with PrOD, but not significantly statistic. We didn't find any improvement in platelet count at SVR compared to baseline in patients treated with LED/SOF+RBV, but on the contrary we identified a slight decrease in platelets that can be explained by splenic sequestration and exaggerated destruction, representing a characteristic status in patients with advanced liver disease. Studies that used radiolabeled platelets have shown a low survival to which is added the low level of thrombopoietin, determined by a decreased synthesis in liver cirrhosis. Tripodi *et al* (14), did not found an appreciable increase in platelet count in their study lot, incriminating the short period of follow-up and the fact that viral eradication and improvement of liver function does not change the splenic pool. None of the currently used coagulation parameters in cirrhotic patients (PT, INR) had a notifiable statistic change. This finding confirms the idea that the anticoagulant status in cirrhotic patients cannot be reflected only by these laboratory parameters.

The majority of biochemical parameters showed an improvement on SVR12 compared to baseline. Transaminases and GGT had significantly decreased values in both groups of patients, revealing the disappearance of continuous liver injury due to the viral clearance. Also, we observed a decreasing trend for MELD score, showing an improvement in global liver function.

The evaluation of the severity of the liver disease according to the Child-Pugh score (CPS) demonstrated that the majority of the patients who had variceal hemorrhage were in the moderate and severe stages (CPS class B/C).

The assessment of the risk of development or of the prognosis of bleeding of esophageal varices, depending on the ratio between the spleen/platelet diameter, showed that the majority of patients who had variceal hemorrhage had a value > 3.

The bleeding events were mostly variceal bleeding, which is in fact and rightly the cause of portal hypertension; despite SVR liver fibrosis remains, portal hypertension remains and thus the risk of bleeding.

The clinical use of hepatic venous pressure gradient (HVPG) measurement is limited by its invasiveness. Moreover, its availability is mostly restricted to academic centers. Thus, the non-invasive monitoring of the regression of liver fibrosis and portal hypertension after HCV eradication will be a major challenge in the post-HCV era.

A well-designed retrospective study conducted by Libânio and Marinho (15), evaluated the changes in HVPG and liver stiffness in 60 cirrhotic patients (84% Child A) treated with various combinations of DAAs. SVR led to a reduction in HVPG in 80% of the patients. This beneficial effect was found in all strata of HVPG, although

portal hypertension was less likely to improve in Child B patients; therefore, a point of no return seems to exist from which viral elimination is no longer capable of preventing portal hypertension progression and liver decompensation.

Although non-invasive methods cannot substitute HVPG measurement, non-invasive evaluation of liver fibrosis by transient elastography (Fibroscan) and serological tests (Fibromax and APRI test) showed that patients with variceal hemorrhage had decreased hepatic stiffness after SVR, but with a preservation value above 12.5 kPa, which shows that liver fibrosis remains after SVR, portal hypertension remains and thus the risk of bleeding (16).

According to Calvaruso V *et al*. (17), although portal hypertension improves in the majority of people with hepatitis C and cirrhosis after hepatitis C is cured, not all patients experience improvement, and esophageal varices may continue to progress despite successful hepatitis C treatment.

What is less clear is how frequently portal hypertension and varices improve after hepatitis C is cured. Two studies presented at The International Liver Congress (Paris, 2018) reported on the evolution of these conditions and attempted to identify predictors of regression or progression (18).

Puente Á *et al.*(19), found that clinically significant hypertension persisted in 68% of people with cirrhosis cured of hepatitis C, despite a significant improvement in liver stiffness. Persistence of portal hypertension was associated with a higher hepatic venous pressure gradient and a smaller reduction in liver stiffness, which involve an increased risk of variceal bleeding.

Another study conducted by Sabela *et al*. (20), showed that once patients develop cirrhosis with severe portal hypertension (HVPG $\geq$ 10 mmHg), regardless of SVR in hepatitis C therapy, they remain at risk for hepatic decompensation within the first 5 years after treatment.

Due to the novelty of DAAs therapies (and thus short follow up times) there are only few studies assessing the effects of HCV novel treatments on portal hypertension and clinical decompensation. In patients successfully treated with DAAs, MELD and CHILD-PUGH scores were shown to improve, fact also demonstrated by the literature data (21).

Future studies should focus on predictors of portal hypertension resolution, as it may influence management and monitoring in the subset of patients with a high probability of having clinically significant portal hypertension after treatment, objectified by the appearance of bleeding causes variceal as well as by the portal hypertensive gastropathy.

CONCLUSIONS

Bleeding events in patients with HCV-related liver cirrhosis treated with DAAs are not influenced by the variations of coagulation parameters, rather correspond to the hemodynamic changes induced by the status of advanced liver disease. It should be underlined that the bleeding events were mostly variceal bleeding, which is in fact and rightly a consequence of portal hypertension; despite SVR liver fibrosis remains, portal hypertension remains and thus the risk of bleeding.

It remains to be further demonstrated if the mechanism of DAAs can influence the development of bleeding events in these patients or are part of the natural course of advanced liver disease.

REFERENCES

1. Shepard CW, Finelli L, Alter MJ (2005) Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; 5: 558-567.
2. Lisman T, Porte JR. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood* 2010; 116(6): 878-885.
3. Huiban L, Muzîca CM, Cuciureanu T, Chiriac S, Mihai F, Sfarti C, Sîngeap AM, Gîrleanu I, Stanciu C, Trifan A. Thrombotic events in patients with hepatitis C virus liver cirrhosis treated with direct acting antivirals and sustained virological response. *Rev Med Chir Soc Med Nat Iaşi* 2018; 122(1): 122-129.
4. Northup PG, Caldwell SH. Coagulation in liver disease: a guide for the clinician. *Clin Gastroenterol Hepatol* 2013; 11(9): 1064-1074.
5. Caldwell SH, Hoffman M, Lisman T, *et al*. Coagulation disorder and hemostasis in liver disease: pathophysiology and critical assessment of current management. *Hepatology* 2006; 44: 1039-1046.
6. Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, Austin A, Ferguson JW, Olliff SP, Hudson M, Christie JM; Clinical Services and Standards Committee of the British Society of Gastroenterology. U.K. guidelines on the management of variceal hemorrhage in cirrhotic patients. *Gut* 2015; 64: 1680-1704.
7. Girleanu I, Trifan A, Cojocariu C, Singeap A, Sfarti C, Stanciu C. The risk of thrombotic events in patients with liver cirrhosis. *Rev Med Chir Soc Med Nat Iasi* 2012; 116(4): 991-996.
8. ***European Association for Study of the Liver. EASL clinical practice guidelines: Management of hepatitis C virus infection. *J Hepatol* 2014; 60: 392-420.
9. Nahon P, Bourcier V, Lavese R, *et al*. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. *Gastroenterology* 2017; 152: 142-156.
10. Mandorfer M, Kozbial K, Schwabl P, *et al*. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. *J Hepatol* 2016; 65: 692-699.
11. Tripodi A, D'Ambrosio R, Padovan L, *et al*. Evaluation of coagulation during treatment with directly acting antivirals in patients with hepatitis C virus related cirrhosis. *Liver Int* 2017; 37(9): 1295-1303.
12. Goldberg D, Ditah IC, Saeian K, *et al*. Changes in the Prevalence of Hepatitis C Virus Infection, Nonalcoholic Steatohepatitis, and Alcoholic Liver Disease Among Patients With Cirrhosis or Liver Failure on the Waitlist for Liver Transplantation. *Gastroenterology* 2017; 152: 1090-1099.
13. ***World Health Organization. Global health sector strategy on viral hepatitis, 2016-2021. Available from: URL: http://www.who. int/hepatitis/strategy2016-2021/ghss-hep/en/, 2016.
14. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2011; 365: 147-156.
15. Libânio D, Marinho RT. Impact of hepatitis C oral therapy in portal hypertension. World J *Gastroenterol* 2017; 14; 23(26): 4669-4674.
16. Lu M, Li J, Zhang T, Rupp LB, *et al*. Chronic Hepatitis Cohort Study Investigators. Serum Biomarkers Indicate Long-term Reduction in Liver Fibrosis in Patients with Sustained Virological Response to Treatment for HCV Infection. *Clin Gastroenterol Hepatol* 2016; 14: 1044-1055.
17. Calvaruso V, *et al*. The course of esophagogastric varices in patients with cirrhosis after DAA-induced HCV clearance. The International Liver Congress, Paris, 2018, abstract FRI-376, 2018. *Journal of Hepatology* 2018; 68: S533.
18. Mandorfer M, *et al*. Resolution of clinically significant portal hypertension after sustained virologic response to interferon-free regimens prevents hepatitis decompensation. The International Liver Congress, Paris, 2018, abstract FRI-380, 2018. *Journal of Hepatology* 2018; 68: S532.
19. Puente Á, Cabezas J, López Arias MJ, *et al*. Influence of sustained viral response on the regression of fibrosis and portal hypertension in cirrhotic HCV patients treated with antiviral triple therapy. *Rev Esp Enferm Dig* 2017;109: 17-25.
20. Sabela Lens, Diego Rincón, Montserrat García-Retortillo, *et al*. Association Between Severe Portal Hypertension and Risk of Liver Decompensation in Patients With Hepatitis C, Regardless of Response to Antiviral Therapy. *Clin Gastroenterol Hepatol* 2015; 13(10): 1846-1853.
21. Trifan A, Stanciu C, Gheorghe L, *et al*. Efficacy and safety of paritaprevir/ritonavir, ombitasvir, and dasabuvir with ribavirin for the treatment of HCV genotype 1b compensated cirrhosis in patients aged 70 years or older. *Medicine (Baltimore)* 2017; 96(50): e9271.