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ABOUT COVER

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ORIGINAL ARTICLE

Observational Study

Management of betablocked patients after sustained virological response in hepatitis C cirrhosis

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Abstract

BACKGROUND

Current guidelines do not address the post–sustained virological response management of patients with baseline hepatitis C virus (HCV) cirrhosis and oesophageal varices taking betablockers as primary or secondary prophylaxis of variceal bleeding. We hypothesized that in some of these patients portal hypertension drops below the bleeding threshold after sustained virological response, making definitive discontinuation of the betablockers a safe option.

AIM

To assess the evolution of portal hypertension, associated factors, non-invasive assessment, and risk of stopping betablockers in this population.

METHODS

Inclusion criteria were age > 18 years, HCV cirrhosis (diagnosed by liver biopsy or transient elastography > 14 kPa), sustained virological response after direct-acting antivirals, and baseline oesophageal varices under stable, long-term treatment with betablockers as primary or secondary bleeding prophylaxis. Main exclusion criteria were prehepatic portal hypertension, isolated gastric varices, and concomitant liver disease. Blood tests, transient elastography, and upper gastrointestinal endoscopy were performed. Hepatic venous pressure gradient (HVPG) was measured five days after stopping betablockers. Betablockers could

Institutional review board statement: The study was reviewed and approved by the Human Research and Ethics Committee at Hospital Universitario La Paz (Madrid).

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be stopped permanently if gradient was < 12 mmHg, at the discretion of the attending physician.

RESULTS

Sample comprised 33 patients under treatment with propranolol or carvedilol: median age 64 years, men 54.5%, median Model for End-Stage Liver Disease (MELD) score 9, Child-Pugh score A 77%, median platelets 77.000 × 10^3/μL, median albumin 3.9 g/dL, median baseline transient elastography 24.8 kPa, 88% of patients received primary prophylaxis. Median time from end of antivirals to gradient was 67 wk. Venous pressure gradient was < 12 mmHg in 13 patients (39.4%). In univariate analysis the only associated factor was a MELD score decrease from baseline. On endoscopy, variceal size regressed in 19/27 patients (70%), although gradient was ≥ 12 mmHg in 12/19 patients. The elastography area under receiver operating characteristic for HVPG ≥ 12 mmHg was 0.62. Betablockers were stopped permanently in 10/13 patients with gradient < 12 mmHg, with no bleeding episodes after a median follow-up of 68 wk.

CONCLUSION

Portal hypertension dropped below the bleeding threshold in 39% of patients more than one year after antiviral treatment. Endoscopy and transient elastography are inaccurate for reliable detection of this change. Stopping betablockers permanently seems uneventful in patients with a gradient < 12 mmHg.

Key words: Hepatitis C virus; Oesophageal varices; Portal hypertension; Betablocker; Variceal bleeding

Core tip: Approximately 1/3 of the patients with baseline cirrhosis and bleeding-risk oesophageal varices, satisfactorily evolve below the bleeding-risk threshold, after curation of chronic hepatitis C. In these patients, the definitive interruption of the preventive medication taken to avoid bleeding seems to be safe.

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INTRODUCTION

Sustained virological response (SVR) after treatment implies substantial changes in many aspects of chronic hepatitis C virus (HCV) infection such as liver histology and biochemistry[1], risk of decompensation[2], development of hepatocellular carcinoma[3], as well as in quality of life and comorbidities[4]. These benefits are independent of the drugs used to reach the SVR[5] and have been well known since the interferon (IFN)–based treatment era[6,7].

However, less information is available about the evolution and management of portal hypertension (PH) after SVR[8,9]. In patients with cirrhosis who have already developed oesophageal varices, IFN-based treatments led to low SVR rates at the risk of severe adverse effects[7,10], and their applicability was scant and therefore limiting with respect to data collection in this population. The fact that IFN-free, direct-acting antivirals (DAA) are not subject to these limitations means that they can be used in this patient population[5]. As a result, new data on the evolution of PH and oesophageal varices after SVR show a benefit in some but not all patients, mainly depending on the severity of baseline PH[9].

Simultaneously, the guidelines of the main hepatological associations and consensus reports are starting to provide some-albeit incomplete-recommendations on optimal management of oesophageal varices after SVR[8,11]. The Baveno VI

Consensus on PH[8] provides recommendations after successful cure of the etiologic agent only for patients with small or no varices at baseline. Specifically, current guidelines do not address post-SVR management of cirrhosis patients receiving betablockers with baseline oesophageal varices. Stopping betablockers inappropriately could provoke a life-threatening bleeding episode. On the other hand, prolonging therapy with betablockers unnecessarily exposes patients to uncomfortable, long-term adverse effects[12,13]. In this study, we analyse the progress of PH after SVR in a population of patients with HCV cirrhosis and baseline oesophageal varices under prophylaxis with betablockers. We also assess associated factors, non-invasive assessment, and the risk of permanently stopping betablockers.

MATERIALS AND METHODS

Study population

We performed a prospective, single-center study (Hospital Universitario La Paz, Madrid, Spain) of patients attending the Gastroenterology and Internal Medicine Departments. The inclusion criteria were age > 18 years, HCV cirrhosis, baseline oesophageal varices under stable long-term treatment with carvedilol or propranolol as primary or secondary bleeding prophylaxis, and SVR after treatment with DAA. The exclusion criteria were pre-hepatic PH (portal or splanchnic vein thrombosis, portal cavernoma), isolated gastric varices, liver disease other than that caused by HCV (including alcohol consumption > 30 g daily), active hepatocellular carcinoma, need for betablockers for other reasons, any limitation to the scheduled study procedures, and pregnancy or breastfeeding.

Cirrhosis was diagnosed before treatment with DAA by means of liver biopsy or transient elastography (TE; > 14 kPa)[14]. Baseline medical charts and video records of endoscopies were reviewed to confirm the indication of betablockers. Varices > 5 mm in size were considered large[15]. All patients under carvedilol were receiving 12.5 mg daily. Propranolol was adjusted to ensure a resting heart rate below 55 beats per minute. Patients taking betablockers as secondary prophylaxis were also periodically undergoing endoscopic band ligation for eradication of varices[11]. SVR was defined as undetectable HCV RNA by means of a sensitive polymerase chain reaction–based technique (Abbott Real-Time HCV assay, Abbott Molecular, Des Plaines, United States; lower limit of detection < 12 IU/mL) at least 12 wk after the end of DAA treatment. The DAAs administered were standard combinations of sofosbuvir, ledipasvir, simeprevir, daclatasvir, ombitasvir, ritonavir-boosted paritaprevir, and dasabuvir, with or without ribavirin. Treatments were administered according to clinical guidelines[16,17].

Study assessments

The data recorded were age, sex, body mass index, baseline characteristics of liver disease before DAA treatment [Child-Pugh score, Model for End-stage Liver Disease (MELD) score, TE value, primary or secondary prophylaxis with betablockers], and date of DAA treatment.

After SVR, we performed routine blood testing, abdominal ultrasound, liver elastography, and upper gastrointestinal endoscopy (UGE) and measured the hepatic venous pressure gradient (HVPG) measurement. The blood test included a complete blood count, albumin, bilirubin, creatinine, international normalized ratio, electrolytes, transaminases, and gamma-glutamyl transpeptidase. Undetectability of HCV RNA was reconfirmed. Ultrasound (Aplio 500®, Toshiba Medical Systems, Japan) was performed to verify portal and splanchnic vein patency, absence of hepatocellular carcinoma, and detection of ascites. Measurement of liver stiffness was performed by TE (Fibroscan®, Echosens, France), as previously described[18]. UGE and baseline video records were reviewed by 2 experienced endoscopists (> 10 years). Oesophageal varices were classified on UGE as absent, small (≤ 5 mm), or large (> 5 mm)[15]. HVPG was determined in accordance with a standardized procedure[19,20]. The dose of betablockers was halved for 1 wk and then completely stopped 5 days before HVPG measurement. Statins and spironolactone were also stopped if taken. HVPG measurements were classified as normal (< 6 mmHg), subclinical PH (SPH; 6-9 mmHg), non-bleeding-risk clinically significant PH (NBR-CSPH; 10-12 mmHg), and bleeding risk CSPH (BR-CSPH; ≥ 12 mmHg)[11,21].

Betablockers could be stopped permanently at the discretion of the attending physician if HVPG < 12 mmHg. Patients were followed every 3 mo and contacted to confirm absence of bleeding in the case of nonattendance at a programmed visit. The remaining patients were followed every 6 mo.

Clinical outcome measures

The primary endpoint was the proportion of patients with HVPG < 12 mmHg. Secondary endpoints were disease- and patient-associated factors for HVPG < 12 mmHg, correlation between UGE classification and BR-CSPH, non-invasive assessment of CSPH and BR-CSPH by elastography techniques in this specific scenario, and bleeding risk associated with permanently stopping betablockers.

Statistical analysis

Continuous variables were reported as mean ± SD or median (25th percentile/75th percentile), while categorical variables were reported as absolute number and percentages. Group comparisons of continuous variables were made using the t test or Mann-Whitney test, depending on the normality of distributions. Intra-individual comparisons were performed using the *t* test for paired samples or Wilcoxon matched-pairs signed rank test. Group comparisons of categorical variables were performed using the chi-square or Fisher's exact test. We evaluated the relationship between TE and PH using the Pearson or Spearman correlation coefficients, as appropriate. The diagnostic performance of liver stiffness was assessed using receiver operating characteristic curves constructed to compare the absence and presence of clinically significant PH and the absence and presence of PH with oesophageal varices bleeding risk. We also determined optimal cut-off values of TE to rule out HVPG < 12 mmHg based on the highest sensitivity and with an acceptable specificity higher than 70%, and to rule in HVPG ≥ 12 mmHg based on the highest specificity with an acceptable sensitivity higher than 70%. Univariable and multivariable logistic regression analyses were performed to identify significant predictors of HVPG < 12 mmHg and < 10 mmHg. All statistical tests were 2-sided, and *P* values < 0.05 were considered to be significant. All analyses were conducted using SPSS Version 24.0 (IBM Corp., Armonk, NY, United States).

Ethics

Written informed consent was obtained from each patient included in the study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Human Research and Ethics Committee at Hospital Universitario La Paz (Madrid).

RESULTS

The study population comprised 33 patients, whose main characteristics are shown in Table 1. Median time from the end of DAA treatment to HVPG measurement was 67 wk (56-83).

HVPG results

Median HVPG was 14 mmHg (10-16); this was < 12 mmHg in 13 patients [39.4%; 95% confidence interval (CI): 24.2-56.4]: NBR-CSPH in 6 (18.2%), SPH in 6 (18.2%), and normal in 1 (3%). In the 20 patients with HVPG ≥ 12 mmHg, the median value was 16 mmHg (14-19). Univariable analysis showed that the only factor significantly associated with an HVPG < 12 mmHg was a decrease in the MELD score of at least 1 point (*P* = 0.045, Table 2).

HVPG-UGE correlation

The correlation between UGE and HVPG as a predictor of bleeding risk was assessed in 27 patients receiving betablockers as primary prophylaxis: Two patients refused to undergo endoscopy, and the four patients receiving betablockers as secondary prophylaxis were excluded from the analysis because of the variceal modifications induced by band ligation. Variceal size had regressed in 19/27 (70%). The correlation with HVPG is shown in Table 3.

Non-invasive assessment by TE

TE was feasible in 28 patients (84.8%). Per protocol, the area under the receiver operating characteristic curve (AUROC) was 0.62 (95%CI: 0.40-0.84; *P* = 0.27) for BRPH and 0.83 (95%CI: 0.66-1; *P* = 0.01) for CSPH. The best TE cut-off to predict CSPH was 19.8 kPa, with a sensitivity of 68%, specificity of 83%, positive predictive value of 94%, negative predictive value of 42%, positive likelihood ratio of 4.1, negative likelihood ratio of 0.38, and accuracy of 0.71. A TE value ≤ 14.9 kPa was sufficient to rule out CSPH with a sensitivity of 90.9%. A TE value ≥ 22.7 kPa was sufficient to rule in CSPH with a specificity of 100%. BRPH values were not calculated taking into account the absence of a statistically significant association in AUROC. Using these CSPH criteria, 19/28 HVPG measurements (67.9%) could have been

Table 1 Patients characteristics

	n = 33
Age (yr), median (P25-P75)	64 (59-73)
Males, *n* (%)	18 (54.5)
BMI > 25 kg/m^2, *n* (%)	26 (78.8)
ALT (UI/L), median (P25-P75)	21 (18-26)
Platelets (× 10^3/μL), median (P25-P75)	77 (58-100)
Total bilirubin (mg/dL), median (P25-P75)	1.1 (0.8-1.6)
Albumin (g/dL), median (P25-P75)	3.9 (3.8-4.1)
Baseline Child-Pugh A/B/C, *n* (%)	25 (75.8)/8 (24.2)/0
HVPG Child-Pugh A/B/C, *n* (%)	30 (90.9)/3 (9.1)/0
Baseline MELD score, median (P25-P75)	10 (9-11)
HVPG MELD score, median (P25-P75)	9 (8-12)
Baseline TE (kPa), median (P25-P75)	24.8 (17.3-34.3)
HVPG TE (kPa), median (P25-P75)	21.7 (16.6-26.8)
Baseline ascites, *n* (%)	12 (36.4)
HVPG ascites, *n* (%)	3 (9.1)
Propranolol/Carvedilol, *n* (%)	14 (46.7)/16 (53.3)
Primary prophylaxis indication, *n* (%)	29 (88)
Large oesophageal varices	26 (79)
Small oesophageal varices + Child-Pugh B	3 (9)
Secondary prophylaxis, *n* (%)	4 (12)

Baseline refers to data before direct-acting antivirals treatment. Hepatic venous pressure gradient (HVPG) refers to results on the day of the haemodynamic study. Baseline ascites or under diuretic treatment for previous ascites. The most recent ligations had been performed at least 10 mo before HVPG. BMI: Body mass index; ALT: Alanine-aminotransferase; HVPG: Hepatic venous pressure gradient; MELD: Model for End-Stage Liver Disease; TE: Transient elastography.

avoided.

Bleeding risk after permanent discontinuation of betablocker

Betablockers were permanently discontinued in 10/13 patients with HVPG < 12 mmHg. In the remaining three patients, treatment was reintroduced immediately after HVPG at the discretion of the attending physicians. All patients attended their scheduled visits. After a median follow-up of 68 wk (62-86), no variceal bleeding episodes were recorded, and no patients developed de novo ascites. One episode of variceal bleeding was recorded in a patient who continued with betablockers as primary prophylaxis 72 wk after HVPG and 4.2 years after the end of DAA treatment. Her gradient was 14 mmHg.

DISCUSSION

Post-SVR management of HCV cirrhosis patients with baseline oesophageal varices receiving prophylaxis with betablockers has not been classified in guidelines or reports. According to our results, more than one third are below the bleeding risk threshold, and permanently stopping betablockers seems to be uneventful.

Other studies have shown a decrease in HVPG to < 12 mmHg after DAA-based SVR in some patients with baseline values above this figure, albeit at a lower rate than in ours. In the study of Afdhal *et al*[22], 4 of the 33 (12%) patients with baseline HVPG ≥ 12 mmHg had HVPG < 12 mmHg at the end of treatment. Mandorfer *et al*[23] found that 29/60 patients with baseline HVPG ≥ 12 mmHg were reassessed a median of 16 wk after the end of treatment, although the authors do not provide specific data on evolution. In the study of Lens *et al*[24], improvement was seen in 142/176 patients (19.2%) at SVR24. In the study by Afdhal *et al*[22], HVPG was determined 48 wk after the end of treatment in 9 patients; in 3 patients (33.3%), HVPG decreased to < 12 mmHg. We observed this decrease in 39.4% (13/33) of the patients in our study a median of 67 wk after the end of treatment. Taken together, these data show a trend toward an increasing number of patients with baseline BRPH below this threshold depending on the time between the end of DAA treatment and measurement of

Table 2 Univariable analysis of factors associated factors with hepatic venous pressure gradient ≥ 12 mmHg

	< 12 mmHg (*n* = 13)	≥ 12 mmHg (*n* = 20)	*P*
Age (yr), median (P25-P75)	63 (55-70)	66 (59-73)	0.44
Males, *n* (%)	8 (61.5)	10 (50)	0.72
BMI > 25 kg/m2, *n* (%)	11 (84.6)	15 (75)	0.67
Baseline albumin (g/dL), median (P25-P75)	3.7 (3.4-3.8)	3.6 (3.2-3.8)	0.54
HVPG albumin (g/dL), median (P25-P75)	3.9 (3.8-4.3)	3.9 (3.8-4.1)	0.33
Δ Albumin (g/dL), median (P25-P75)	0.4 (0.1-0.8)	0.3 (0.1-0.5)	0.59
Δ Albumin (%), median (P25-P75)	11.8 (2.6-21.6)	9 (2.5-18.2)	0.58
Baseline platelets (× 103/μL), median (P25-P75)	88 (58-92)	58 (44-82)	0.19
HVPG platelets (× 103/μL), median (P25-P75)	79 (62-100)	74 (57-101)	0.59
Δ Platelets (× 103/μL), median (P25-P75)	5000 (-5000-17000)	6500 (-4000-17000)	0.89
Δ Platelets (%), median (P25-P75)	7.1 (-7.5-17.2)	10.9 (-8.4-28.3)	0.50
Baseline Child-Pugh A/B/C, *n* (%)	10 (76.9)/3 (23.1)/0 (0)	15 (75)/5 (25)/0 (0)	1
HVPG Child-Pugh A/B/C, *n* (%)	11 (84.6)/2 (15.4)/0 (0)	19 (95)/1 (5)/0 (0)	0.54
Δ Child Pugh	0 (-1-0)	-0.5 (-1-0)	0.59
Baseline MELD score, median (P25-P75)	10 (9-11)	10 (8-11)	0.58
HVPG MELD score, median (P25-P75)	9 (8-10)	10 (8-12)	0.50
Δ MELD score, median (P25-P75)	-1 (-1-0)	0 (-1-1.5)	0.045
Baseline TE (kPa), median (P25-P75)	21.1 (15.6-32)	27.7 (18.4-34.3)	0.39
HVPG TE (kPa), median (P25-P75)	20.3 (14.1-24.5)	23.3 (17.9-29.9)	0.31
Δ TE (kPa), median (P25-P75)	-6.2 (-10.7-2.1)	-4.3 (-7.8-3.4)	0.51
Δ TE (%), median (P25-P75)	-26.7 (-40.7-12.4)	-13.8 (-29.6-21.8)	0.69
Baseline ascites, *n* (%)	4 (30.8)	8 (40)	0.72
HVPG ascites, *n* (%)	1 (7.7)	2 (10)	1
BB prophylaxis, *n* (%)			0.13
Primary	13 (100)	16 (80)	
Secondary	0	4 (20)	

Baseline refers to data before direct-acting antivirals treatment. Hepatic venous pressure gradient refers to results on the day of the haemodynamic study. Baseline ascites or under diuretic treatment for previous ascites. BMI: Body mass index; HVPG: Hepatic venous pressure gradient; MELD: Model for End-Stage Liver Disease; TE: Transient elastography; BB: Betablockers; Δ: delta.

HVPG. The findings seem to indicate that regression of PH after SVR is a dynamic process. Univariable analysis showed that the only factor associated with a decrease below the bleeding risk threshold was a ≥ 1-point decrease in the MELD score. We found no association with the Child-Pugh score, liver stiffness, or albumin, as reported elsewhere[22-24], probably because we analysed an absolute value (< 12 mmHg), whereas other authors used a percentage result (10%-20% decrease from baseline).

One of our aims was to evaluate the accuracy of nonhemodynamic assessment of these patients, that is, without cumbersome, invasive HVPG measurements. Other studies have used endoscopy to evaluate the progress of varices after SVR but without performing HVPG[25,26]. Based on our results, endoscopy does not seem to be reliable. Variceal size regressed in 70% of patients, although HVPG remained above 12 mmHg in 12/15 patients with small or no varices. This would have led to an inaccurate and dangerous underestimation of bleeding risk. On the other hand, since 2/12 patients with HVPG < 12 mmHg had large varices, stratification was, once again, inaccurate. TE results were also disappointing for evaluation of the bleeding risk threshold, with a non–statistically significant AUROC of 0.62 for ≥ 12 mmHg. The poor performance for this cut-off has been reported elsewhere[27], thus supporting the notion that TE performs worse as PH increases[28]. Results are more reliable for a cut-off of ≥ 10 mmHg, with an AUROC of 0.82 (P = 0.01). Evaluating the 10-mmHg threshold by TE can be used to establish bleeding risk, since it is obviously below 12 mmHg and possesses high predictability for ruling in and ruling out risk, although patients with PH between 10-12 mmHg would go undetected. Two thirds of HVPG measurements could have been avoided with high reliability using this threshold. Our results agree with those reported elsewhere[23,24,27]. Finally, betablockers were stopped in 10/13

Table 3 Correlation between upper gastrointestinal endoscopy and hepatic venous pressure gradient

n = 27 (%)	No varices	Small varices	Large varices	Total
HVPG < 12 mmHg	1 (3.7)	9[1] (33.3)	2 (7.4)	12
HVPG ≥ 12 mmHg	1 (3.7)	11[2] (40.7)	3 (11.1)	15
	2	20	5	27

[1]Two patients with baseline small oesophageal varices + Child-Pugh B;
[2]One patient with baseline small oesophageal varices + Child-Pugh B. HVPG: Hepatic venous pressure gradient.

patients with HVPG < 12 mmHg, with no bleeding episodes after more than one year of follow-up. Since this is a firmly established cut-off, no bleeding is expected in patients below this threshold[11,29,30]. Our results reinforce this as a valid criterion not only in patients with active HCV disease, but also after SVR. In contrast with reports from other authors[31], we did not record ascites in this group after stopping betablockers.

Our study is subject to two main limitations. Firstly, the number of patients is relatively small. However, to our knowledge, ours is the only report that comprehensibly evaluates such a specific group of patients. For instance, only seven patients with large oesophageal varices were included for HVPG measurement in the study of Mandorfer *et al*[23] and 38 in that of Afdhal *et al*[22]. The correlation between UGE and HVPG and permanent withdrawal of betablockers was not evaluated either of these studies or in that of Lens *et al*[24]. Our second limitation is the lack of a baseline hemodynamic study. HVPG measurement is not compulsory in clinical practice for betablockers to be started[8,11]. Virtually all patients with large oesophageal varices or with small varices and decompensated cirrhosis have an HVPG > 12 mmHg[24,32-35]. The percentage decrease in PH was not evaluated and was therefore not available. This is a good prognostic factor of future variceal bleeding[11,29,30,36], although patients with a > 10%-20% decrease in HVPG still maintain some bleeding risk[29]. Therefore, a percentage decrease only is an inadequate criterion for safe discontinuation of betablockers and an absolute result above or below 12 mmHg is necessary to ensure accurate decision-making.

In conclusion, 39% of HCV cirrhosis patients with baseline oesophageal varices receiving betablockers to prevent bleeding are below the bleeding risk threshold more than one year after DAA-based SVR. The correlation between endoscopy and HVPG is weak after SVR and cannot be advocated as a safe decision-making tool. Similarly, TE does not correlate well with the hemodynamic bleeding risk threshold of 12 mmHg, although it can be used to reliably detect CSPH. Permanent interruption of betablockers in patients with an HVPG < 12 mmHg seems to be uneventful.

ARTICLE HIGHLIGHTS

Research background

Baveno VI Consensus addresses management of patients without baseline oesophageal varices, or with small varices, in whom aetiological factor has been removed. No recommendation is given in those under betablockers. Main Liver Associations Guidelines on this topic simply refer to Baveno.

Research motivation

Future research in this field should confirm our results in a larger number of patients. Alternative aetiologies, not only hepatitis C virus (HCV) cirrhosis, should be explored.

Research objectives

We tried to satisfy a real-life, unmet situation: how to manage betablockers in our patients after sustained virological response (SVR).

Research methods

All our study patients were recruited from our clinic. Baseline data [before direct-acting antivirals (DAA) treatment] were collected and checked against evolutionary data after SVR. As a novelty, endoscopy variceal size was confronted to hepatic venous pressure gradient having in mind endoscopy has been advocated by some authors to be a reliable tool after SVR. Transient elastography was also challenged in this SVR setting.

Research results

After more than one year of SVR, 39% of our patients evolved below the oesophageal bleeding threshold. The only predictable factor of this favourable evolution was a drop of at least 1 point in Model for End-Stage Liver Disease score. Transient elastography and endoscopy did not confidently detect this change. In those patients below 12 mmHg, permanently stopping betablockers was safe as no bleeding episode has appeared after more than one year of follow-up. Main remaining problem is the evolution of those patients still above 12 mmHg. Portal hypertension regression seems to be a dynamic condition after SVR. Therefore, some of them could still evolve satisfactorily in future evaluations but others could have reached a point of no return.

Research conclusions

After more than one year of SVR, 39% of patients with baseline HCV cirrhosis and oesophageal varices under prophylactic betablockers are below the bleeding threshold. Transient elastography and endoscopy are unreliable in this setting. Permanently stopping betablockers seems to be safe in those below 12 mmHg. Evolution of portal hypertension after SVR in the subgroup of patients under betablocker treatment. Unreliability of transient elastography and endoscopy in this setting. Safety of permanently stopping betablockers in those below 12 mmHg. Portal hypertension can regress even in those with the more severe condition, making prophylaxis with betablockers unnecessary. Several studies recently characterize portal hypertension evolution in the new scenario of easy-to-reach SVR after interferon-free DAA treatment. Data on the evolution of portal hypertension and its management in those patients with the more severe condition (*i.e.*, under betablockers) were lacking. Betablockers can be permanently stopped in those below 12 mmHg after SVR. Non-invasive assessment of post-SVR bleeding threshold is not reliable. Portal hypertension in those with the more severe condition is a dynamic regressive process with a clinical benefit for patients. Severe portal hypertension regresses in some patients and betablockers can be safely stopped. Endoscopy and transient elastography are not reliable assessing post-SVR bleeding risk. Betablockers can be safely discontinued in those below 12 mmHg.

Research perspectives

Do not trust non-invasive assessment of bleeding risk after SVR. Reliable tools for non-invasive assessment of bleeding risk after removal of aetiological factor. We presume combinatory algorithm with liver and spleen elastographies. Perhaps ultrasound-based contrast-enhanced arrival time to hepatic vein.

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