Selected Summaries

Beta-blockers in cirrhosis: Do they have benefits beyond the prevention of variceal bleeding?

Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja JL, Aracil C, Banares R, Morillas RM, Poca M, Penas B, Augustin S, Abraldes JG, Alvarado E, Torres F, Bosch J. (Hospital of Santa Creu and Sant Pau, Autonomous University of Barcelona, Hospital Sant Pau Biomedical Research Institute [IIB Sant Pau] Barcelona, Spain; Centre for Biomedical Research in Liver and Digestive Diseases Network [CIBERehd]; Ramón y Cajal University Hospital, Ramón y Cajal Institute of Health Research [IRYCIS], University of Alcalá, Madrid, Spain; Liver Unit, Valld'Hebron University Hospital, Valld'Hebron Research Institute [VHRI], Autonomous University of Barcelona, Barcelona, Spain.) β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): A randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2019;**393:**1597–608.

SUMMARY

Decompensation of cirrhosis carries a dismal prognosis. The risk of decompensation, i.e. development of variceal bleeding, ascites or hepatic encephalopathy, increases once clinically significant portal hypertension (CSPH)—defined as hepatic venous pressure gradient (HVPG) of more than 10 mmHg—occurs. Beta-blockers are known to induce a reduction in HVPG. Their administration is beneficial in patients with variceal bleeding, but has not been found to be useful in patients with early portal hypertension. The aim of this double-blind randomized controlled trial, carried out in eight hospitals in Spain, was to assess whether treatment with beta-blockers in the middle stage of cirrhosis—after the appearance of CSPH but before the appearance of features of decompensation—can prevent decompensation or death.

Between January 2010 and June 2015, a total of 631 patients with compensated cirrhosis were screened. Several patients were excluded for various reasons, such as a history of previous decompensation; presence of high-risk oesophageal varices; prior treatment with beta-blockers, nitrates, anticoagulants or antiviral drugs for hepatitis C; age <18 years and >80 years; baseline bilirubin >3 mg/dl; contraindications to beta-blockers; or a coexisting illness limiting life expectancy. Of the remaining 293 patients who underwent HVPG measurement, 210 had CSPH; of these, 9 withdrew from further study. The remaining 201 patients were categorized into two groups, based on acute HVPG response, i.e. >10% reduction in HVPG from the baseline, at 20 minutes after the administration of 0.15 mg/kg intravenous propranolol, as responders and non-responders. The participants were randomly assigned to receive a placebo or a beta-blocker. Responders in the beta-blocker group received propranolol (40–60 mg/day), and any non-responders received carvedilol (6.25–25 mg/day); for each drug, the dose was based on prior titration in individual patients to attain the highest dose that permitted heart rate of above 55 beats/minute and systolic blood pressure >90 mmHg.

Patients were followed up clinically at 1 month, at 3 months and every 6 months thereafter, and HVPG was measured annually. The primary outcome was time to decompensation of cirrhosis (development of ascites, variceal bleed or overt hepatic encephalopathy) or liver-related death. The secondary outcomes were development of individual complications of portal hypertension, adverse events and overall survival.

Over a median follow-up period of 37 months, decompensation or death occurred in 16% of 100 patients receiving beta-blockers and 27% of 101 placebo recipients. The major difference in the two groups was a decrease in the incidence of ascites (9% in the beta-blocker group *v.* 20% in the placebo group). Annual HVPG measurements revealed a mean decrease of 11% (2.1 mmHg) from the baseline values in the beta-blocker group, but no change in the placebo group. Two-thirds of the patients developed high-risk oesophageal varices during the study and underwent endoscopic variceal ligation. In a *post-hoc* exploratory analysis that excluded patients with bleeding, beta-blocker group still had better outcomes. Compliance rates and overall side-effect profiles were similar in the two groups. The authors concluded that in patients with compensated cirrhosis and CSPH, beta-blockers can prevent the occurrence of decompensation.

COMMENT

Cirrhosis of liver has several stages which evolve over several years—beginning with a compensated stage, appearance of features of decompensation (viz. ascites, variceal bleed and hepatic encephalopathy), followed by more serious complications (such as spontaneous bacterial peritonitis and hepatorenal syndrome) and culminating in death unless liver transplantation is done. Nearly 50% of patients with compensated cirrhosis develop ascites within 10 years of follow-up.[1] Patients who develop ascites have 1- and 5-year mortality rates of 15% and 44%, respectively.[2]

Cirrhosis is associated with several circulatory alterations, including a hyperdynamic circulation, splanchnic vasodilatation, effective reduction of circulatory volume, increased heart rate, cardiac output and sodium and fluid retention.[3] These circulatory changes are believed to contribute to the development of decompensation and complications of cirrhosis. Thus, in patients with compensated cirrhosis, HVPG >10 mmHg is independently associated with the development of ascites and oesophageal varices.[4] Beta-blockers can counteract this hyperdynamic circulation by blockade of beta-1 and beta-2 receptors in the heart and blood vessels, respectively. Their administration is associated with a reduction in HVPG and reduced risk of bleeding in patients with varices.[5,6] However, their administration in an earlier stage of disease, i.e. before varices have developed, does not prevent the appearance of large varices. Similarly, in patients with advanced cirrhosis with refractory ascites and/or hepatorenal syndrome, administration of beta-blockers is associated with increased mortality.[7] Hence, it appears that there is a window period in the natural history of cirrhosis, during which (but not before or after) beta-blockers are beneficial. Delineation of this window period is a major challenge in clinical practice. This trial (the PREDESCI trial) explored this issue, i.e. whether administration of beta-blockers in patients with cirrhosis and CSPH but no prior decompensation can reduce the risk of liver decompensation or death.

In this study, administration of beta-blockers was associated with a reduced risk of occurrence of a composite outcome consisting of one or more features of liver decompensation or of death. Given the randomized, double-blind study design, its

results provide a compelling reason for using beta-blockers in patients with compensated cirrhosis similar to those included in the study. However, the study also had certain limitations, suggesting a need for caution in the routine use of beta-blockers in the specific situation studied.

First, the study results are unlikely to be generalizable. Of the patients screened, only about one-third fulfilled the inclusion and exclusion criteria, implying that the study population were a highly select group. Despite cirrhosis being a common clinical condition, the authors could enrol only 201 patients from eight hospitals over a 42-month period, i.e. fewer than one patient per hospital per month. Thus, the intervention will need to be applied selectively. It is notable that the authors used HVPG measurement as a selection criterion. This measurement is invasive and costly, and not performed as a routine in patients with cirrhosis in most of the hepatology centres around the world, particularly in India.

Two different types of beta-blockers were used, with the choice being guided by the response of HVPG to an intravenous dose of beta-blocker during the haemodynamic study. The need for these procedures limits the clinical utility of the study. Application of this study's results would have been easier if the authors had used a simpler and more widely available surrogate marker for CSPH, for example, presence of varices instead of HVPG, and had not chosen the beta-blocker agent based on haemodynamic response to intravenous beta-blocker. Carvedilol was associated with a greater HVPG reduction, despite being used in patients who were 'non-responders' to beta-blockers during the haemodynamic study, and could have been used in all the patients. Although the authors state that the effect of two drugs on the primary outcome was similar, one must bear that the sample size was too small to detect any such difference between propranolol and carvedilol, and one could expect the latter drug to perform better.

Second, the conclusion based on the study's primary efficacy measure, a reduction in the occurrence of decompensation or death—a composite outcome—by nearly half, may be an overstatement. The use of composite outcomes, by combining several different outcomes and thus a higher event rate, permits a smaller sample size. However, such outcomes also pose challenges in the interpretation of study results.[8] It has been argued that, in a composite outcome, all the components should be of similar importance, as far as possible. The primary outcome in this study included time to events as disparate as ascites and liver-related death. The median survival after the first appearance of ascites is around 5 years, indicating that these outcomes are a mixed bag. In fact, the major difference between the treated and the placebo groups was in the occurrence of ascites, a condition that can often be treated successfully with dietary salt restriction and a small dose of diuretics, and not in those of more serious events such as occurrence of hepatic encephalopathy or death. Furthermore, a perusal of time-to-event curves in the two groups shows that the two curves almost overlapped during the initial 24 months and diverged thereafter; this indicates that beta-blockers bestowed little benefit during the initial 24 months of follow-up and any benefit was delayed beyond this time point.

Third, though the relative reduction in hazard of decompensation or death was around 50%, the absolute reduction in these events was only around 10%. Thus, the number needed-to-treat to benefit 1 patient over a median 37-month follow-up was between 9 and 10, a relatively large number. This suggests a need to find markers that can help identify the patients most likely to benefit from beta-blockers. The authors did undertake a sensitivity analysis to identify such markers but failed to find any. However, the power of the study for such analyses was too low, and future larger studies may be helpful.

Finally, the most common cause of cirrhosis in this study was hepatitis C, but these patients had not received treatment for hepatitis C. Since the time this study started, direct-acting antiviral agents have become the standard of care for patients with hepatitis C, including those with cirrhosis. Such treatment is known to reduce HVPG and risk of future decompensation.[9] Whether beta-blockers would provide any additional benefit beyond that associated with successful treatment for hepatitis C remains unclear. With antiviral treatment halting further progression of liver fibrosis, any benefit of beta-blocker administration may be much smaller.

Thus, in conclusion, this study expands the window period for the use of beta-blockers in patients with cirrhosis to another phase of this disease, i.e. when CSPH has developed but large varices have not appeared. However, based just on this study, it would be difficult to unequivocally recommend beta-blockers in such patients. We believe that future studies are essential; these can be on similar lines, but using less invasive and more easily available surrogate markers of CSPH, such as the presence of varices or of liver stiffness measurement,[10,11] and using one specific beta-blocker. If these studies confirm the benefit, we would have a useful intervention for patients with cirrhosis. Moreover, if these studies help in identifying the predictors for response to beta-blockers, that would be an added benefit.

Conflicts of interest. None declared

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