

Prevention of Variceal Rebleeding: Endoscopes, Drugs, and More

SEE ARTICLE ON PAGE 461

Variceal bleeding is a serious complication of portal hypertension and a leading cause of death in patients with cirrhosis.¹ The patients who survive an initial episode have a risk of rebleeding approaching 80% at 2 years.^{1,2} Thus, therapy to prevent rebleeding is widely endorsed, to the point that trials including a no-treatment or placebo arm are considered ethically indefensible.^{3,4} One result is that studies of combination therapy will be increasingly the norm.⁵⁻¹⁰ The study by Lo et al., published in this issue of *HEPATOLOGY*,⁵ reflects this trend. The authors report that the combination of endoscopic band ligation (EBL), nadolol, and sucralfate is superior to EBL alone in preventing rebleeding (from any source and from esophageal varices). The authors found a reduction in transfusion requirements during follow-up, reduced recurrence of varices after initial obliteration, and even a trend toward improved survival.

The rationale behind the use of combination therapy is that agents acting through different mechanisms may be additive in terms of their benefit or even synergistic.⁶ Recent years have seen major progress in understanding the pathophysiologic mechanisms leading to portal hypertension due in part to experimental rat models.⁴ A key concept concerns the hyperdynamic circulation in cirrhosis,^{11,12} which increases both portal venous inflow and portal pressure. This provides the rationale for the use of nonselective β -blockers (such as propranolol or nadolol) to prevent initial or recurrent variceal bleeding¹³: these vasoactive agents reduce portal pressure by decreasing splanchnic blood flow and the hyperdynamic circulation.^{14,15} Randomized controlled trials and meta-analyses have confirmed their benefit.^{9,16-18}

Another key concept is that the increased intrahepatic vascular resistance of cirrhosis is due not only to fixed anatomical changes inherent to cirrhosis but also to active contraction of vascular smooth muscle cells and the abundant myofibroblasts present in the scar tissue and, possibly, activated hepatic stellate cells.^{19,20} This active contraction involves reduced production of the endogenous vasodilator, nitric oxide, by hepatic endothelial cells and overexpression of endogenous vasoconstrictors (endothelins, leukotrienes, and activated neurohumoral systems).^{21,22} The dynamic component

can be counteracted in part by vasodilators,¹⁹ including the nitric oxide donors nitroglycerin²³ and isosorbide-5-mononitrate (ISMN),²⁴ adrenergic antagonists such as prazosin,²⁵ angiotensin blockers such as losartan, and anti-endothelins.²⁶ A problem with vasodilators as therapy, however, is that they may cause systemic vasodilation, reducing arterial pressure and peripheral resistance, and aggravating renal dysfunction and sodium retention in cirrhotic patients with ascites.^{25,26}

Another step forward was the demonstration that when the hepatic venous pressure gradient (HVPG) is below 12 mm Hg, the risk of bleeding from varices is essentially nil.²⁷ A drop of more than 20% from baseline HVPG also is associated with a very low residual risk of variceal rebleeding in patients treated with β -blockers.²⁸ Unfortunately, nonselective β -blockers achieve these target reductions in HVPG in only about one third of patients.^{14,28} Hence, the introduction of combined pharmacologic therapy.^{7,29} It was proposed that propranolol or nadolol (which reduces HVPG by decreasing splanchnic blood flow) in combination with low-dose ISMN (which decreases HVPG by reducing hepatic resistance) would be superior to either agent alone. The combination was postulated to be additive in reducing portal pressure, whereas β blockade would exert mild systemic vasoconstrictor effects, preventing most of the adverse vasodilatory effects of ISMN.²⁹ Subsequent trials have confirmed the synergistic effect of this drug combination on the HVPG,⁷ its lack of significant adverse effects on renal function,³⁰ and its increased efficacy in the prevention of recurrent variceal bleeding.³¹

A variation on combined therapy consists of endoscopic obliteration of varices together with a portal hypotensive agent such as propranolol or nadolol.^{10,17} The goals are to reduce the risk of rebleeding during the course of initial endoscopic therapy (which is actually the period with the higher risk of rebleeding)² and to decrease the risk of recurrent varices and rebleeding after initial endoscopic therapy is completed.¹ Previous studies suggested that the combination approach achieves better results than either treatment alone, and this was confirmed by meta-analysis,^{9,10} although the small size of the studies weakened the conclusions.⁹ Now that sclerotherapy has been replaced almost universally by EBL,¹⁰ the combination of EBL and β -blockers was the next logical step.

The results of Lo et al.⁵ with this combination, while encouraging, carry some caveats: (1) the study was not double-blind and, therefore, is subject to observer bias; (2) the study was conducted in a single center, which entails possible selection bias; (3) serial measurements of HVPG were not performed, which would have established whether the clinical benefit from combination therapy was caused by a decrease in HVPG and the degree to which HVPG must be decreased to realize a benefit comparable with that of EBL alone; and (4) the use of sucralfate as part of the combination therapy is difficult to evaluate without an appropriate control group.

The first concern (observer bias) is probably unavoidable in assessing procedures until future technological improvements allow for a "blind" endoscopist. This disadvantage,

Abbreviations: EBL, endoscopic band ligation; ISMN, isosorbide-5-mononitrate; HVPG, hepatic venous pressure gradient.

From the Liver Unit, IMD, Hospital Clinic and IDIBAPS (Institut de Investigació Biomèdica August-Pi-Sunyer), University of Barcelona, Barcelona, Spain.

Received June 21, 2000; accepted July 5, 2000.

Supported by grants 00/0044 from Fondo de Investigación Sanitaria and SAF99-0007, Dirección General de Enseñanza Superior e Investigación Científica.

Address reprint requests to: Jaime Bosch, M.D., Hepatic Hemodynamics Laboratory, Liver Unit, Hospital Clínic, C Villarroel 170, 08036 Barcelona, Spain. E-mail: jbosch@medicina.ub.es.

Copyright © 2000 by the American Association for the Study of Liver Diseases.

0270-9139/00/3203-0033\$3.00/0

doi:10.1053/jhep.2000.16663

however, does not apply to pharmacologic treatments, which can be adequately masked by using identical placebos. Observer bias usually works in favor of the "new" treatment: future trials may be less positive than this one. The second concern (selection bias) can contaminate any study but is more likely in single-center unblinded studies in which entry and exclusion criteria may be less well-defined than in cooperative trials.³ HVPG measurements are important, not only in terms of understanding the mechanism of the treatment effect on the main study end point (variceal rebleeding), but also for understanding the factors influencing recurrence of varices after initial "obliteration," frequency of eradication, and incidence of other complications of portal hypertension on follow-up, such as ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome, all of which may be favorably influenced by a reduction in HVPG.^{1,9} Moreover, because portal pressure may decrease spontaneously during the follow-up, changes in HVPG may influence the results in the group treated with EBL alone, as shown for patients treated with sclerotherapy.³¹ Finally, adding a second drug (sucralfate) without a specific control group is problematic, although the results suggest that it did not influence the outcome, because the number of patients bleeding from esophageal ulcers was not significantly different in the treatment arms. More rational would be addition of a second portal hypotensive agent such as ISMN.^{7,29}

Until multicenter prospective double-blind studies are available, shall we change our way of treating patients in the light of the results of the study by Lo et al.? It is my personal view that the evidence presented, although encouraging, falls short of definitive. Comparable results have been reported for other treatment combinations, such as nadolol plus ISMN,³¹ or with other procedures (*i.e.*, TIPS and surgery).^{17,32} The available data do not permit an informed choice among these treatments. Combination therapy may be preferred in patients on single therapy who experience a rebleeding episode (even if not "clinically significant").⁹ The combination of an endoscopic procedure, such as EBL, and a nonselective β -blocker would appear to be the first choice assuming no contraindications to the β -blocker. Otherwise, alternatives should be considered, including drug combinations, TIPS, distal splenorenal shunt, calibrated small-diameter mesocaval or portacaval shunt, and conjoint use of injection sclerotherapy and EBL.^{9,10}

JAIME BOSCH, M.D.
Liver Unit
IMD
Hospital Clinic and IDIBAPS
University of Barcelona
Barcelona, Spain

REFERENCES

- Bosch J, Burroughs AK. Clinical manifestations and management of bleeding episodes in cirrhotic patients. In Rodés J, McIntyre N, Benhamou JP, Bircher J, Rizzetto M, eds: Oxford Textbook of Clinical Hepatology Oxford: Oxford University Press, 1998;671-693.
- Graham DY, Smith JL. The course of patients after variceal haemorrhage. *Gastroenterology* 1981;80:800-809.
- De Franchis R, ed. Portal Hypertension II. Proceedings of the second Baveno International Consensus Workshop on Definitions, Methodology, and Therapeutic Strategies. Oxford: Blackwell Science, 1996.
- Grace ND, Groszmann RJ, Garcia-Tsao G, Burroughs AK, Pagliaro L, Makuch RW, Bosch J, et al. Portal hypertension and variceal bleeding: an AASLD single topic symposium. *HEPATOLOGY* 1998;28:868-880.
- Lo GH, Lai KH, Cheng JS, Chen MH, Huang HC, Hsu PI, Lin CK. Endoscopic variceal ligation plus nadolol and sucralfate (Triple Therapy) compared with ligation alone for the prevention of variceal rebleeding: a prospective, randomized trial. *HEPATOLOGY* 2000;32:461-465.
- García-Pagán JC, Escorsell A, Moitinho E, Bosch J. Influence of pharmacological agents on portal hemodynamics: basis for its use in the treatment of portal hypertension. *Semin Liver Dis* 1999;19:427-438.
- García-Pagán JC, Feu F, Bosch J, Rodes J. Propranolol compared with propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis. A randomized controlled study. *Ann Int Med* 1991;114:869-873.
- Albillos A, García-Pagán JC, Iborra J, Bandi JC, Cacho G, Pérez-Paramo M, Escorsell A, et al. Propranolol plus prazosin compared with propranolol plus isosorbide-5-mononitrate in the treatment of portal hypertension. *Gastroenterology* 1998;115:116-123.
- D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis* 1999;19:475-505.
- DeFranchis, Primignani M. Endoscopic treatments for portal hypertension. *Semin Liver Dis* 1999;19:439-473.
- Vorobioff J, Bredfeldt JE, Groszmann RJ. Hyperdynamic circulation in a portal hypertensive rat model: a primary factor for maintenance of chronic portal hypertension. *Am J Physiol* 1983;244:G52-G57.
- Vorobioff J, Bredfeldt JE, Groszmann RJ. Increased blood flow through the portal system in cirrhotic rats. *Gastroenterology* 1984;87:1120-1123.
- Lebec D, Poynard T, Bernuau J, Bercoff E, Nouel O, Capron JP, Poupon R, et al. A randomized controlled study of propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a final report. *HEPATOLOGY* 1984;4:355-358.
- Bosch J, Mastai R, Kravetz D, Bruix J, Gaya J, Rigau J, Rodes J. Effects of propranolol on azygos venous blood flow and hepatic and systemic hemodynamics in cirrhosis. *HEPATOLOGY* 1984;4:1200-1205.
- Lebec D, Hillon P, Muñoz C, Goldfarb G, Nouel O, Benhamou JP. The effect of propranolol on portal hypertension in patients with cirrhosis: a hemodynamic study. *HEPATOLOGY* 1982;2:523-527.
- Poynard T, Cales P, Pasta L, Ideo G, Pascal JP, Pagliaro L, Lebec D, et al. Beta-adrenergic-antagonists in the prevention of first gastrointestinal bleeding in patients with cirrhosis and oesophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. *N Engl J Med* 1991;324:1532-1538.
- D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension. A meta-analytic review. *HEPATOLOGY* 1995;22:332-354.
- Bernard B, Lebec D, Mathurin P, Opolon P, Poynard T. Beta-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. *HEPATOLOGY* 1997;25:63-70.
- Bathal PS, Groszmann HJ. Reduction of the increased vascular portal resistance of the isolated perfused cirrhotic rat liver by vasodilators. *J Hepatol* 1985;1:325-327.
- Pinzani M, Gentilini P. Biology of the hepatic stellate cells and its possible relevance in the pathogenesis of portal hypertension in cirrhosis. *Semin Liver Dis* 1999;19:397-410.
- Gupta TK, Toruner M, Chung MK, Groszmann RJ. Endothelial dysfunction and decreased production of nitric oxide in the intrahepatic microcirculation of cirrhotic rats. *HEPATOLOGY* 1998;28:926-931.
- Wiest R, Groszmann RJ. Nitric oxide and portal hypertension: its role in the regulation of intrahepatic and splanchnic vascular resistance. *Semin Liver Dis* 1999;19:411-426.
- Groszmann RJ, Kravetz D, Bosch J, Glickman M, Bruix J, Bredfeldt J, Conn HO, Rodes J, et al. Nitroglycerin improves the hemodynamic response to vasopressin in portal hypertension. *HEPATOLOGY* 1982;2:757-762.
- Navasa M, Chesta J, Bosch J, Rodes J. Reduction of portal pressure by isosorbide-5-mononitrate in patients with cirrhosis. Effects on splanchnic and systemic hemodynamics and liver function. *Gastroenterology* 1989;96:1110-1118.
- Albillos A, Lledo JL, Rossi I, Perez-Paramo M, Tabuena MJ, Bañares R, Iborra J, et al. Continuous prazosin administration in cirrhotic patients: effects on portal hemodynamics and on liver and renal function. *Gastroenterology* 1995;109:1257-1265.
- Groszmann RJ. Beta-adrenergic blockers and nitrovasodilators for the treatment of portal hypertension: the good, the bad, the ugly. *Gastroenterology* 1997;113:1794-1797.
- Groszmann RJ, Bosch J, Grace ND, Conn HO, Garcia-Tsao G, Navasa M, Alberts J, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990;99:1401-1407.

28. Feu F, Garcia-Pagan JC, Bosch J, Luca A, Teres J, Escorsell A, Rodes J. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet* 1995;346:1056-1059.
29. Garcia-Pagán JC, Navasa M, Bosch J, Bru C, Pizcueta MP, Rodés J. Enhancement of portal pressure reduction by the association of isosorbide-5-mononitrate to propranolol administration in patients with cirrhosis. *HEPATOLOGY* 1990;11:230-238.
30. Morillas RM, Planas R, Cabré E, Galán A, Quer JC, Feu F, García-Pagán JC, Bosch J, Gassull MA. Propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis: long-term hemodynamic and renal effects. *HEPATOLOGY* 1994;20:1502-1508.
31. Villanueva C, Balanzò J, Novella M, Soriano G, Sainz S, Torras X, Cussò X, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal bleeding. *N Engl J Med* 1996;334:1624.
32. Burroughs AK, Patch D. Transjugular intrahepatic portosystemic shunt. *Semin Liver Dis* 1999;19:457-473.