

Combination therapy reverses effects of portal hypertension in rats

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A combined treatment with rapamycin and Gleevec might reverse the effects of portal hypertension in patients with chronic liver disease, according to the results of a new study on rats. The study is in the October issue of *Hepatology*, a journal published by John Wiley & Sons on behalf of the American Association for the Study of Liver Diseases (AASLD).

Portal hypertension is a serious complication of chronic liver disease, and a leading cause of liver transplantation and mortality. It develops when a blockage in the blood flow through the liver causes the body to develop new blood vessels to develop (through a process called angiogenesis) across the esophagus and stomach. These new vessels drain into the portal vein, worsening the portal blood pressure and contributing to the formation of life-threatening complications like esophageal varices. Prior studies have suggested that anti-angiogenic treatment might help prevent the progression of the portal hypertension syndrome.

Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are crucial to angiogenesis, so researchers, led by Mercedes Fernandez of the IDIBAPS in Barcelona, examined the effects of VEGF and PDGF inhibitory drugs on rats with established portal hypertension, to best mimic the typical human patient. They treated portal vein-ligated rats with rapamycin (VEGF signaling inhibitor), Gleevec (PDGF signaling inhibitor) or both simultaneously, and determined the effects on hyperdynamic splanchnic circulation and

portosystemic collateralization.

In rats whose portal hypertension was fully developed, the combined therapy significantly reduced splanchnic neovascularization and pericyte coverage of neovessels. The rats experienced a 40 percent decrease in portal pressure, along with a 30 percent decrease in superior mesenteric artery blood flow and a 63 percent increase in superior mesenteric artery resistance. This was “a significant reversal of the hemodynamic changes provoked by portal hypertension in rats,” the authors report.

They found that the magnitude of the effects of the combination treatment was superior to the addition of the effects of either drug alone, suggesting that the two worked together to mediate the maintenance of the vascular and circulatory abnormalities observed in rats with portal hypertension.

This is the first study to show that portal hypertension development is associated with a progressive overexpression of PDGF as well as VEGF. It also revealed that anti-angiogenic therapy could not merely prevent, but also revert, abnormalities associated with portal hypertension which would be a very helpful for treating patients with portal hypertension, because they are typically only diagnosed when their condition causes clinical problems. Furthermore, both drugs tested in this study have already been broadly used to treat human malignancies.

“Our results provide new insights into how angiogenesis regulates portal hypertension by demonstrating that the maintenance of increased portal pressure, hyperkinetic circulation, splanchnic neovascularization and portosystemic collateralization is regulated by VEGF and PDGF in portal hypertensive rats,” the authors conclude. “An extended anti-angiogenic strategy (i.e. targeting VEGF/endothelium and PDGF/pericytes) may represent a novel approach in the treatment of portal hypertension.”

Source: John Wiley & Sons, Inc.

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