ABSTRACT

TITLE: Emricasan (IDN-6556) administered orally for 28 days lowers portal pressure in patients with compensated cirrhosis and severe portal hypertension

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ABSTRACT BODY: Abstract Body (Late-Breaking Submission): Caspases play a central role in apoptosis and inflammation. They produce hemodynamically-active, pro-inflammatory microparticles that appear to contribute to the vasodilatation that maintains and enhances portal hypertension in cirrhosis. Emricasan, a pan-caspase inhibitor, has been shown to lower portal pressure and improve survival in a murine model of portal hypertension. The aim of this study was to assess whether emricasan could lower portal pressure in patients with compensated cirrhosis. Methods: This proof-of-concept, multicenter, open-label study enrolled 23 subjects with compensated cirrhosis and portal hypertension (hepatic venous pressure gradient [HVPG] >5 mmHg) at 9 U.S. sites. Emricasan (25 mg) was given orally twice a day for 28 days. HVPG measurements were standardized and a single expert read all HVPG tracings. Results: Median age of subjects was 59 (range 49-80) and 70% were male. Cirrhosis etiologies were mainly NASH and HCV, with 20 (87%) subjects being Child A and having median MELD score of 8 (range 6-15). 22 completed the study. Overall, there were no significant differences in median HVPG before and after emricasan (13.5 vs 13.0 mmHg, respectively). However, when patients were stratified by the recognized HVPG therapeutic threshold of 12 mmHg (indicative of more severe portal hypertension), a significant (p<0.003) decrease in HVPG by 17.2% was noted only in those with an HVPG ≥12 mmHg, who had a mean (SD) decrease of 3.7 (4.0) mmHg. Notably, 4/12 had a ≥20% decrease; 8/12 had a ≥10% decrease; and in 2/12 the HVPG decreased below 12 mmHg. Ten patients with HVPG <12 mmHg had a non-significant (p=0.12) mean (SD) increase of 1.9 (3.2) mmHg. Sensitivity analysis using an HVPG cutoff of 10 mmHg yielded similar results. There were no significant changes in blood pressure or heart rate. AST and ALT levels decreased significantly in the entire group and in those with an HVPG ≥12 mmHg. Overall, serum levels of cCK18 and caspase 3/7 (markers of microparticles and apoptosis, respectively) decreased significantly. Emricasan was well-tolerated with 1 subject discontinuing the study early for non-serious adverse events. One subject had 3 SAEs 10 days after the last emricasan dose, assessed as unrelated to treatment. Conclusion: Emricasan administered orally for 28 days was associated with a significant decrease in portal pressure in patients with compensated cirrhosis and severe portal hypertension. Although a hemodynamic mechanism cannot be ruled out, concomitant decreases in AST/ALT suggest an intrahepatic anti-inflammatory effect. Potential additional long-term effects due to microvascular remodeling will require further investigation.

(No Image Selected)

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