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EDITORIAL

Testing Beneficial Therapy in Human Cirrhosis Using Animal Models of Cirrhosis

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The study by Minuk and colleagues entitled "Daily Ciprofloxacin Treatment for Patients with Advanced Liver Disease Awaiting Liver Transplantation Reduces Hospitalizations" [1] tested the hypothesis that patients on the liver transplant list may benefit from antibiotics as a method of enhancing hepatic regeneration and improving liver function. The authors had previously shown in a rat model of acute and subacute liver failure that antibiotics improved survival [2, 3] and that antibiotics appeared to also improve survival in a model of chronic liver injury [4]. This benefit correlated in these animal models with improvement in markers of hepatic regeneration. In the current study, the authors asked whether the same benefit might be found in cirrhotic patients on the liver transplant waiting list.

This single-site, prospective, randomized, double-blind study measured routine markers of hepatic function (albumin, bilirubin, and international normalized ratio for prothrombin time [INR]), markers of hepatic inflammation (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), and clinical outcomes (hospitalizations, hepatic encephalopathy, etc.) after 1 or 3 months of treatment with placebo or ciprofloxacin 250–500 mg twice daily. Results showed no systematic benefit at 1 or 3 months in markers of hepatic function or inflammation, and a significant improvement in albumin at 1 month was not confirmed at 3 months. However, it should be noted that more precise measurements of hepatic function [5, 6] or markers of regeneration might have shown subclinical benefits that would have been encouraging for further studies. Potential benefits in hospitalizations and clinical outcomes were also assessed. There were fewer hospitalizations for hepatic encephalopathy among subjects receiving ciprofloxacin, but little benefit for other clinical outcomes. As the authors note, antibiotics are helpful in treating encephalopathy and in prophylaxis against spontaneous bacterial peritonitis [7–10]. The effect of antibiotics on improvement in survival among variceal bleeders has been profound [11]. Thus, the reduction in hospitalizations among patients receiving antibiotics in this study is not surprising, and hepatic regeneration is not required to explain this improvement. Thus, the benefits of antibiotics in animal models of acute and chronic liver injury were not confirmed in this clinical trial among patients with advanced cirrhosis on the liver transplant waiting list.

Animal models have been very useful in the evaluation of the pathophysiology of portal hypertension, ascites and hepatic fibrosis [12–17]. Why was so little benefit observed when antibiotics were used in humans with cirrhosis as compared with animal models? The answer partially lies in the difference between changes in pathophysiology in animal models of acute liver injury and humans with cirrhosis, who have dense hepatic fibrosis that develops over long periods of time and resolves slowly when the insult is stopped [18, 19]. By contrast, animal models of cirrhosis generally require continued liver injury to produce cirrhosis, and fibrosis resolves rapidly if the insult is stopped [12–17]. Furthermore, there is often a complex interaction of factors contributing to hepatic injury that includes bacterial products such as endotoxin from the gut that may be less important in man [12–14]. Antibiotics markedly decrease injury in most animal models [12–14]. Therefore, study of the pathophysiology of liver injury and complications of liver disease in animal models has been very

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valuable, but the regression of liver fibrosis differs between humans and animals. Thus, findings in animal models must be confirmed in clinical settings, and we applaud the authors for testing their hypothesis in humans [1]. Unfortunately, this study shows that antibiotics do not enhance hepatic regeneration or improve clinical outcomes by means of regeneration in patients on the liver transplant list.

According to several recent studies, there is no experimental model that completely reproduces human liver fibrosis [12–14]. Since there are contraindications to serial liver biopsies in humans with liver disease, studies of genetic and molecular aspects of liver injury and fibrosis should continue. An initial approach should involve exploration of the molecular mechanisms of liver fibrosis in different diseases [20]. This might elucidate areas of potential efficacy of ciprofloxacin and other fluoroquinolones. Ultimately, all benefits in animals must be confirmed by clinical trials in man.

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