

Cirrhosis is less cirrhosis without virus C

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Article commented

Van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, et al. Association between sustained virological response and all-cause mortality among patient with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; 308: 2584-93.

COMMENTS

In the current commented article, van der Meer, *et al.* demonstrated that sustained virological response in patients with advanced fibrosis was associated with lower overall mortality, lower liver-related mortality including liver failure and liver cancer. No patient achieving sustained virological response required liver transplantation and liver-related mortality was more than 15 times lower (30 *vs.* 2%). Hepatocellular carcinoma rate was also reduced in comparison with non-responders but a significant risk remained. Cumulative HCC occurrence was 5.1% at 10 years *vs.* 21.8% in non-SVR. Genotype 3a, type 2 diabetes mellitus, older age, male gender, heavy alcohol consumption and histological cirrhosis were associated with increased risk of liver cancer.¹

Sustained virological response, the negativity of HCV RNA at 6 months after the end of therapy, is a stable condition and it has been accepted as synonymous of cure of chronic hepatitis C. However, whether the meaning is the same in cirrhosis remains controversial. The inability of the virus to become

part of the human genome allowed antiviral drugs to eradicate the infection. Genetic, metabolic, viral and environmental factors influenced fibrosis progression, but in patients with chronic hepatitis C, HCV RNA replication remains as the major factor, mainly because its eradication has been related to fibrosis or even cirrhosis regression.² HCV eradication has been associated with decreased 10 years mortality near three times and more than 15 times liver-related mortality supporting the idea that virus clearance allowed to the liver to restore hepatic function, even in cirrhotics. Previous data supported an improvement of liver function after sustained virological response but this prolonged follow-up allowed the author to demonstrate how big was the gap between responders and non-responders. Interestingly, none of patients with SVR underwent liver transplantation. Hepatitis C is the major cause of liver transplantation indication in USA and thus, its effective eradication could avoid liver transplantation. In addition, hepatocellular carcinoma in HCV infected patients showed more aggressive tumour features in comparison with non-alcoholic steatohepatitis-related HCC.³ In the sequence hepatitis C infection, HCV replication, hepatic stellate cell activation, fibrosis progression, cirrhosis stage, liver failure, hepatocellular carcinoma, liver transplantation and death, if we attack the beginning we can control the disease and its complications, encouraging us to treat and cure our patients. Protease inhibitors boceprevir and telaprevir increased sustained virological response in patients infected by genotype 1 between 24% and 31% in comparison with standard of care. Thus, triple therapy could improve survival in patients with hepatitis C and advanced fibrosis and it should be started as soon as possible. The higher SVR the better survival.

In spite of genotype 3a showed greater SVR rate than genotype 1 or 4 when treated with peginterferon alpha plus ribavirin, patients with hepatitis C genotype 3 showed higher risk for liver failure and hepatocellular carcinoma highlighting that interferon sensitivity was not related to prognosis. Mo-

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reover, age and cirrhosis stage were also found associated with hepatocellular carcinoma. Thus, prioritization rules should be revisited and easy-to-cure patients should be treated at early stages to increase SVR and decrease HCC risk.

Diabetes mellitus has been proposed as an independent risk factor for hepatocellular carcinoma.⁴ Metformin use has been associated with decreased risk of HCC.⁵ It has been suggested that hyperinsulinemia, caused by insulin resistance, increases insulin like growth factor 1 (IGF-1), which is one of the most powerful activators of cellular proliferation via the AKT/MTOR signaling pathway.⁶ Insulin also activates the intrinsic tyrosine kinase of insulin receptor, by phosphorylation of insulin-receptor substrate-1 (IRS-1). Both IGF-1 and IRS-1 are overexpressed in tumor cells, because they generate, ultimately, inhibition of apoptosis. Furthermore, insulin resistance leads to increased release of multiple proinflammatory cytokines, including TNF α and IL-6, which promote the development of hepatic steatosis, inflammation and subsequent cancer within the liver.⁷ Reactive oxygen species (ROS) are also produced and impair mitochondrial respiration and cause oxidative damage to the mitochondrial genome, activating the apoptosis cascade.⁸ The ability of metformin to reduce insulin levels and to activate cellular AMPK represents, respectively, its direct and indirect proposed anti-oncogenic mechanisms.⁹ Metformin increases beta oxidation and reduces the hepatic gluconeogenesis via activation of AMPK pathway; decreases intestinal glucose absorption; and increases glucose uptake in skeletal muscle.¹⁰ On the other hand, phosphorylated AMPK suppresses the AKT/MTOR signaling pathway, inhibiting cell proliferation.¹¹ Furthermore, AMPK activated actions may be mediated by other multiple pathways, including up-regulation of the p53 and reduction of cyclin D1 levels.¹² Therefore, after the virus was cleared in a cirrhotic patient we need to take care of diabetes and alcohol consumption.

In conclusion, eradication of hepatitis C virus in cirrhotics improves overall survival and virtually eliminates the need for liver transplantation. Liver cancer remains an issue and requires specific approach in cirrhotics despite sustained virological response. The prevalence of more advanced liver disease as well as the total cost associated with care

of chronic hepatitis C is expected to increase in the coming years. Effective anti-HCVtherapies could modulate disease progression and its associate cost.¹³ Antiviral treatment is mandatory in cirrhotics, and also in patients infected by genotype 3a. Alcohol consumption should be avoided and diabetes mellitus controlled. Further studies are warranted to define the optimal management of type 2 diabetes in patients with cirrhosis.

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