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Cell-based therapy to reverse advanced alcoholic liver fibrosis

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Article commented:

Suk KT, Yoon JH, Kim MY, Kim CW, Kim JK, Park H, Hwang SG, *et al*. Transplantation with autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: Phase 2 trial. *Hepatology* 2016. Doi: 10.1002/hep.28693 [Epub ahead of print].

Comment:

Cirrhosis is a leading cause of mortality worldwide, responsible for approximately 800,000 deaths in 2004.[1] Liver transplantation is the only efficacious option for end-stage liver cirrhosis. However, it is limited by donor availability, surgical complications, immunological rejection and high medical costs.[2] Because of these limitations, there has been a focus on therapies for advanced liver fibrosis. Abstinence from alcohol and the new therapies for cure of viral hepatitis C can halt the progression of fibrosis in chronic liver disease and in some cases lead to remodeling of the damaged liver with improvement in liver function. This has given hope that therapies can be created to help boost the regenerative and remodeling capacity of the liver in the absence of ongoing chronic injury.[3] Furthermore, in some cases these therapies could be used as a means of bridging a patient with cirrhosis to liver transplantation if needed.

Cell based therapy has also shown some promise as a means to treat patients with cirrhosis. Cells from the bone marrow have been shown to play a role in the resolution of liver fibrosis and there have been several studies seeking to use bone marrow cells to stimulate liver regeneration and reduce fibrosis. Bone marrow contains hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), which can differentiate into either hepatocyte-like cells as well as myofibroblastic cells.[3,4] These hepatocyte-like cells can then help with remodeling of the cirrhotic liver. HSCs have been successfully extracted in the form of $CD34^+$ cells after administration of granulocyte-colony stimulating factor (G-CSF).[5] These cells express certain hematopoietic markers that allow them to differentiate into epithelial cells such as hepatocytes. Certain studies have shown improvement in albumin levels as well as Child-Pugh scores, but the mechanism to improve liver damage remains unclear.[5,6] The mechanisms of MSCs has been better defined than that of HSCs. MSCs have the ability to differentiate into hepatocyte-like cells and secrete trophic factors that reduce inflammation and apoptosis of damaged cells. Furthermore, they can secrete growth factors that stimulate angiogenesis and tissue regeneration. Finally, they appear to have a direct effect on hepatic stellate cells and decrease collagen synthesis.[7-10]

In a recent issue of *Hepatology*, Suk, *et al*. investigated the efficacy and safety of autologous MSC transplantation in the treatment of alcoholic cirrhosis.[11] The rationale for this is based on the fact that MSC infusion has led to improvements in liver histology in patients with liver cirrhosis secondary to viral hepatitis. The authors of the current study have focused their attention on the effect of MSC infusions on alcoholic cirrhosis. In a previous pilot study, they were able to show histologic improvement in this type of patient.[11] In this phase 2 study, the authors included 72 patients with Child-Pugh B or C alcoholic cirrhosis and randomized them to receive no MSC transplantation and either one or two infusions of MSCs. No patients with extremely severe liver dysfunction (i.e. MELD > 20) were included. Liver biopsies were performed just prior to stem cell transplantation and then 6 months after enrollment. The authors found a statistically significant reduction in the amount of collagen seen on

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liver biopsy for those patients that received MSC transplantation. There was no change in fibrosis score when one-time transplantation was compared to two-time. The secondary endpoint also saw a statistically significant reduction in the Child-Pugh score of approximately one point. Importantly, the authors did not find significant side effects in patients treated with MSC infusion. The results of the study strongly suggest that cell-based therapies could be useful in reversing cirrhosis in patients with advanced fibrosis in which the causative agent (i.e. alcohol intake) is inactive.

Developing effective therapies to reverse advanced fibrosis is an urgent need in clinical hepatology. Currently, most viral hepatitis can be controlled or cured with oral therapies. Furthermore, patients with self-inflicted liver diseases, such as alcoholic liver disease, can change employ behavioral and lifestyle interventions so the cause of liver injury is attenuate or even removed. There are several reports showing that in patients in whom the cause of liver disease is removed (i.e. sustained viral response to chronic hepatitis B or C), there is a significant decrease in liver fibrosis.[12-15] However, reversibility of fibrosis in patients with advanced cirrhosis can be hampered by the presence of insoluble collagen (cross-linked) and avascular areas with regenerative nodules. It is possible that for these types of patients, cell-based therapies, rather than pharmacological approaches, are more effective to regress liver fibrosis. The encouraging results in the study by Suk, *et al.* supports this assertion. There are, however, several limitations in this study that deserve attention. First, the possibility of inducing hepatocellular carcinoma after the use of stem cells in patients with cirrhosis is an important concern that needs to be carefully addressed by longer follow-up studies using sensitive techniques (i.e. MRI). Second, the study did not clearly differentiate between compensated cirrhosis with preserved synthetic function and no complications of portal hypertension versus patients with impaired function and active complications (i.e. ascites). It is conceivable that the strategy to treat both groups of patients is quite different. Patients with compensated cirrhosis would especially benefit from anti-fibrotic therapies that can be achieved be increasing the number of collagen-degrading cells in the fibrotic liver. In contrast, patients with decompensated cirrhosis and impaired liver function basically need regeneration of the hepatocellular mass. In addition, cell-based therapies should target important determinants of portal hypertension other than fibrosis. These components include endothelial dysfunction, pro-thrombogenic microenvironment and splanchnic vasodilatation. Further studies exploring these other mechanisms are warranted. Finally, the clinical benefits of this type of therapy needs to be explored in more detail in longer follow-up studies. Improvements in the Child-Pugh score after stem cell infusions is promising, but it is important to determine if this directly translates to decreased complications of cirrhosis, including ascites and hepatocellular carcinoma. We hope this promising study by Suk stimulates future phase 3 trials that demonstrate the benefits and side effects of MSCs in cirrhotic patients. Furthermore, we hope other studies emerge that investigate the molecular events induced by different types of cell-based therapies.

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