Mesenchymal stem cell based therapeutic intervention against viral hepatitis: A perspective

Vikas Saxena
University of Maryland, Baltimore, USA

*Corresponding Author:
Vikas Saxena DVM, Ph.D.
Center for Vascular and Inflammatory Diseases, School of Medicine, University of Maryland, Baltimore, MD 21201, USA
Tel: +1-614-607-4216
Email: VSaxena@som.umaryland.edu

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Abstract

Viral hepatitis is the seventh leading cause of mortality around the world resulting in 1.5 million deaths annually. Acute viral hepatitis is mostly self-limiting in nature, but chronic infection leads to liver failure and hepatocellular carcinoma. In those cases, liver transplantation is indicated. Limited supplies of donor livers require development of alternative approaches. Use of mesenchymal stem cells as a source of hepatocyte in cases of viral hepatitis is discussed.

Keywords: Viral Hepatitis; Hepatitis A; Hepatitis B; Hepatitis C; Hepatitis D; Hepatitis E; Liver Transplantation; Mesenchymal Stem Cells.

Abbreviation: HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HDV: Hepatitis Delta Virus; HEV: Hepatitis E Virus; DAA: Direct Acting Antiviral.

Opinion

The liver is an important organ of the body. Being nutrient rich, it is also a target for several infectious diseases. Infectious viral hepatitis, which is inflammation of liver due to viral infection, is the seventh leading cause of mortality around the world [1]. There are five major classes of viruses inducing hepatitis: hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], hepatitis Delta virus [HDV] and hepatitis E virus [HEV]. HAV, an RNA virus, is transmitted mainly through fecal-oral route by ingestion of contaminated food. HBV, a DNA virus, is transmitted through exposure to contaminated blood, semen and other body fluids. HBV can also be transmitted from mother to child at the time of birth. HCV, an RNA virus, and like HBV, can be transmitted through exposure to infective blood and blood products. HDV is a satellite RNA virus to HBV, i.e. HDV infections occur only in those who are already infected with HBV. Dual infection of HBV and HDV results in more serious disease and worse outcome. HEV, an RNA virus, is mostly transmitted through consumption of contaminated food and water.

All these infectious hepatotropic viruses induce hepatitis that pose a greater challenge to health worldwide. HAV and HEV are endemic viruses in several low incomes, third-world countries. Viral hepatitis is generally acute and self-limiting in nature. However, it can turn in to a chronic form of infection, mostly in Immunocomprised individuals or under immune suppressed conditions e.g. in a solid organ transplant recipient undergoing immunosuppressive drug treatment, which may lead to fulminant hepatitis and liver failure. Viral hepatitis induced by HBV and HCV more commonly progress towards liver cirrhosis which leads to fibrosis and poses an increased risk of hepatocellular carcinoma or liver cancer. HAV, HBV, and HEV are controllable due to availability of vaccines; however, in 2011 vaccine against HEV was licensed in China only, and is not widely available. There is no vaccine available against HCV; however, recent developments of direct acting antiviral [DAA] drugs led to an important breakthrough. These new drugs can cure viral infections in most patients.

Despite availability of vaccine and drugs, there has been a steady increase in the number of deaths worldwide attributable to viral hepatitis. According to an estimate, between 1990-2013
there was an increase of 63% deaths due to viral hepatitis of which 96% were due to HBV and HCV. There were 1.5 million deaths due to viral hepatitis in year 2013 alone [1].

Liver transplantation is recommended treatment for end-stage liver diseases. However, in the cases of viral hepatitis, viral recurrence after liver transplantation is a universal phenomenon. It is more so because the use of immunosuppressive drugs required during solid organ transplantation, which renders host more vulnerable to spread of viral infection. Use of antivirals before and after liver transplantation has been recommended, but these antivirals have several side effects. Also, it is complicated, with availability of an appropriate liver donor as well as transplant rejection. Therefore, safe, cost effective, and practical alternatives to liver transplantation, especially in cases of viral hepatitis, are under investigation.

Mesenchymal stem cell [MSC] based therapeutic intervention holds promise to overcome several challenges in hepatic transplantation. MSCs are adherent, fibroblast-like cells with the ability of self-renewal and to differentiate into multiple mesenchymal cell lineages such as osteoblasts, chondrocytes, adipocytes, and importantly, hepatocytes [2]. MSCs can be derived from a variety of tissues, such as umbilical cord bone marrow, trabecular bone, synovial membrane, and fetal tissues such as lung, pancreas, spleen and liver, etc. [3-6]. By culturing MSCs in chemically-defined media, they can differentiate into hepatocyte-like cells possessing liver-specific genes and functions [3, 7]. In animal models of liver injury, hepatic engraftment of transplanted MSCs highlight clinical potential of MSCs in the treatment of liver diseases in general and viral hepatitis in particular [8, 9]. Since identification of MSCs as a source for hepatocyte, a standardized procedure in compliance with current Good Manufacturing Practices has been formulated to ensure the safety, quality, and identity of cell products [6]. MSC-derived hepatocyte as source of hepatocyte transplantation are in clinical practice. Peng et. al. [10] had used HBV patient-derived autologous marrow MSCs and transplanted them through proper hepatic artery. It leads to a short-term improvement in patients’ liver health. However, improvements are needed in the long term.

Recently Wang et al. [11] made attempts to obtain MSCs from liver. It was found that liver-derived human MSCs [LHMSCs] are partially committed towards development into hepatocytes and produce pro-angiogenic, anti-inflammatory, and anti-apoptotic cytokines. LHMSCs were found to contain MSC-like properties in form of morphology, immune functions and differentiation. By growing LHMSCs in defined media authors were able to generate hepatocytes; however, their clinical significance needs to be assessed. Studies of this kind give hope for the development of an effective hepatocyte pool to be used in cases of terminal liver failure.

Transplantation of stem cell derived hepatocytes poses its own challenges. There are chances that injected cells may proliferate in other organs. By injecting cells directly into the liver or through hepatic artery and also by modifying MSCs via expression of liver-specific homing receptors, this challenge can be overcome. Hepatocytes derived from MSCs need to have a standard evaluation to assess their potential as fully functional primary hepatocytes. Such evaluation parameters need to be developed and standardized. Another important question is to know how many cells to inject in a particular disease. The evaluation criterion should include recommendation on number of cells to be injected in a particular disease based on the damage sustained by the liver. Finally, in cases of viral hepatitis, there are chances that virus may infect newly transplanted hepatocytes. Therefore, a treatment regimen comprising pre- and post-transplantation viral suppression or clearance will be required. By analyzing all above aspects in empirical manner, hepatocyte transplantation in cases of liver failure could soon become an effective therapeutic regimen.

Thus overall, viral hepatitis is a big burden on public health being the leading cause of deaths worldwide. Despite availability of vaccines and drugs to treat and control specific pathogens, alternative methods of treatment, especially at the end-stage of viral hepatitis progression provides an important opportunity to improve public health. Liver transplant is one of the options and among them mesenchymal stem cell derived hepatocytes gives new hope to the patients.

References