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Narrative Review

Stem Cell Therapy for Liver Cirrhosis - Prospects and challenges

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Abstract:
The burden of liver diseases and their impact on health is a global concern. While liver transplant remains the curative option for end-stage liver diseases, it has many shortcomings restricting its widespread availability and adaptation. The quest for an effective alternative to slow down progression of liver cirrhosis and restoration of function of cirrhotic liver is therefore ongoing, where stem cell therapy is on the table which. However, although in many cases the results are encouraging with stem cells in liver diseases, it still has a long way to go before it can be recommended in regular clinical practice. We have significant experience of treating liver cirrhosis patients with human progenitor stem cells. Here we present a blend of our own experience and review of recent literature to assess where we stand today with stem cells as an option at our disposal for treating liver diseases.
Keywords: Stem cell, liver cirrhosis.

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Introduction:

There are approximately 500 million people in the world who are at risk of developing liver cirrhosis and complications.[1,2] Liver diseases were responsible for over 1.3 million deaths globally in 2017; 1-year mortality being 57%.[3,4] It has been estimated that these diseases account for 2.4% of the global death burden .[4] At present, liver transplantation remains the only curative option for end-stage liver disease. However, it has several limitations, like shortage of organs, organ rejection and high cost .[5,6] Patients on waiting list awaiting donor organ, have high mortality rate.[7,8] Moreover, liver transplantation is still not available in Bangladesh. Liver support devices like, MARS act as 'bridge' to transplant, but studies have shown that these devises including MARS do not reduce mortality significantly compared to standard medical care .[9]

On the other hand, the potential of stem cells to differentiate into multiple cell lines makes it a potential candidate to induce regeneration in failing organs, particularly the liver which has excellent regenerative capacity .[10,11] Contrary to our previous understanding, we now know that liver cirrhosis is not completely irreversible and therefore stem cells may represent an option for restoration of normal or near normal liver function even in established liver cirrhosis.[12, 13, 14, 15] Besides, stem cell therapy will have several advantages over liver transplantation. A donor will be able to donate stem cells to multiple recipients. The technique is simple and cost effective compared to liver transplantation and there will be no need to remove the recipient liver.[16]

The history of cell therapy for liver diseases dates back to 1976 when allogenic hepatocyte transplantation was performed via portal vein in congenital enzyme deficient rat.[17] Later hepatocytes were transplanted into spleen. The hypothesis was that spleen would play the role of ectopic liver.[18] Subsequently in humans, in end-stage liver disease, hepatocytes transplanted via splenic artery remained viable and the post-transplant spleen displayed hepatic cord structure.[19]

Discussion:

Mesenchymal stem cells

Mesenchymal stem cells (MSC)s is mesoderm derived pluripotent stem cells. They can be isolated from bone marrow, umbilical cord, fat, pulp, placenta, endometrial tissue, limbus and amniotic membrane. MSCs have several advantages like multi-directional differentiation, immunomodulatory and pro-angiogenic effect, secretion of growth factors, cytokines and regulators through paracrine signaling and other pathways.[20, 21] They decrease the expression of inflammatory molecules like interleukin-12 (IL-12) and tumor necrosis factor-α (TNF-α), while secreting interferon-ϒ (IFN-ϒ) and IL-10. This leads to an increase in the number of regulatory T cells.[22] They also increase CCL18 and improve monocyte survival.[23] They improve anti-inflammatory effect of macrophage by secreting prostaglandin E2 (PGE2),stimulated gene/protein 6 and indolemine 2,3-deoxygenase (IDO) and inhibit antibody production, secretion and proliferation of activated B lymphocytes.[24, 25, 26] It has also been observed that MSCs inhibit non-apoptotic death of hepatocytes by ferroptosis by decreasing intra-cellular reactive oxygen species (ROS) and ferrous level.[27] Another advantage with MSCs is that these do not induce host immune response due to low immunogenicity.[21] MSCs express specific cell surface markers, like CD105, CD73 and CD90 and can improve immune response [28]. All these, in turn, may contribute to hepatic regeneration. Besides, MSCs are associated with low risk of carcinogenicity.[29]

MSCs secrete IL-10, which inhibit activation of hepatic stellate cells (HSC) and extracellular matrix (ECM) formation during hepatic regeneration. MSCs also induce apoptosis of HSC through FasL pathways.[30] Macrophages are crucial in hepatic fibrosis as they secrete fibrotic factors like transforming growth factor-β (TGF-β) and platelet derived growth factor (PGDF).[31, 32] Macrophages are characterized as pro-inflammatory or M1type and pro-repair or M2 type.[33] MSCs polarize macrophages to M2 state and promote their death.[34, 35, 36] Thus, MSCs reduce hepatic inflammation and fibrosis. Therefore, it is no wonder that till 2022, there were around 1300 publications in PubMed and more than 50 clinical trials registered in ClinicalTrials.gov using MSCs in treating liver diseases.

A phase II clinical trial with autologous bone marrow derived MSCs in 71 alcoholic liver cirrhosis patients has shown improvement of liver function and fibrosis and Child-Pugh and Model for End Stage Liver Disease (MELD) scores compared to control group, however no significant difference was observed between single and double MSC infusions.[37] Another study involving 110 acute on chronic liver failure (ACLF) patients also reported improvement of

liver function and MELD score, better infection control and reduced mortality at 24 weeks follow up.[38] A Chinese group has extensively studied MSCs in wide range of liver diseases including decompensated liver cirrhosis, primary biliary cholangitis (PBC), ACLF and liver transplant recipients. They have observed improvement in liver function and hepatic functional reserve in addition to reduced transplant rejection and post-transplant complications and improvement of quality of life and survival.[39, 40, 41, 42] Besides, at 75 month follow up, none of the 219 liver cirrhosis patients who received MSC therapy developed hepatocellular carcinoma (HCC).[43]

MSCs also improve complications of liver cirrhosis like, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy and hepatic failure.[44,45,46] In fact, a meta-analysis showed that MSCs are associated with statistically significant improvement in serum albumin and total serum bilirubin in decompensated liver cirrhosis.[47] Furthermore, significant reduction of serum biomarkers of hepatic fibrosis namely, procollagen III C terminal peptide, procollagen III N terminal peptide (PIIINP), serum laminin, hyaluronic acid and type IV collagen following MSC infusion have also been reported.[48,49] Having said so, it needs also be mentioned that there are several published studies in the literature, which failed to reveal any improvement of liver function with MSC.[50,51,52] Such inconsistencies may be attributed to source of MSC, sample size, inclusion and exclusion criteria, study end point etc. Another limitation with MSC therapy is that the mechanism of MSC induced improvement in liver diseases have been studied only in vitro and not in humans, as technical and ethical issues remain concern.[53,54]

Haemopoietic progenitor stem cells:

MSCs therapy however remains challenging for resource constrained countries like Bangladesh, as extremely high tec, sophisticated and expensive instruments and good manufacturing practice (GMP) are pre-requisite for MSC therapy. This is also clearly defined in the national guideline on stem cell and cell based products of Bangladesh Government.[55] In such a scenario, haemopoietic progenitor stem cells provide a visible option. These improve the damaged liver through paracrine signaling between donor and host cells, which induces cytokines and growth factors.[56,57,58] After partial hepatectomy in humans, haemopoietic progenitor stem cells have shown to reduce IL-1 mediated inflammation on one hand, while on the other hand facilitate CD39 dependent liver regeneration.[59]

Granulocyte colony stimulating factor (GCSF) is a haemopoietic growth factor that mobilizes haemopoietic progenitor stem cells to peripheral circulation.[60] GCSF induced proliferation of haemopoietic progenitor stem cells have shown to induce hepatic regeneration in acute and chronic liver damage models.[61,62]

In one of our studies involving 34 decompensated liver cirrhosis patients, we saw improvement in ascites and serum albumin following infusion of haemopoietic progenitor stem cells via hepatic arterial route.[63] We had similar experience after administrating haemopoietic progenitor stem cells via portal venous route in 20 more decompensated liver cirrhotics via portal venous route.[64] In both studies, the mortality appeared to be low. In a large study, it was demonstrated that GCSF in combination with haemopoietic progenitor stem cells infusion improved liver function, Child-Pugh score and survival in acute liver failure.[65] In addition, human menstrual blood stem cells have shown to reduce progression of hepatic fibrosis in animal model.[66] Besides, researchers from our region have shown that the CD34 cell population rises in the liver following GCSF administration.[67] Studies from our region have also found that GCSF administration leads to improvement in Child-Pugh and MELD scores, prevents development of sepsis and hepato-renal syndrome and improves survival in decompensated cirrhosis.[12,13] He also had satisfactory results with GCSF injections in a group of 17 decompensated cirrhosis patients.[68]

Improvement in serum albumin level has also been reported following MSC infusion. A meta-analysis demonstrated that there was significant improvement in serum albumin following both intravenous and hepatic arterial infusion of MSCs compared to control group [47]. The exact explanation of the improvement in serum albumin level in our patients is difficult to explain. Only human albumin injection does not improve serum albumin and ascites so drastically as experienced by us. It tempts us to hypothesize that combination of human albumin and haemopoietic progenitor stem cells may have potentiating impact on ascites.[63]

None of our patients developed HCC. A study found that umbilical cord-derived MSC infusion is also not associated with increase in frequency of HCC.[69]

Other types of stem cells:

Clinical trials with human embryonic stem cells (hESCs) have ethical and legal concerns as these cells are associated with carcinogenesis and immune rejection.[53] Similar issues are also associated with induced pluripotent stem cells (iPSCs).[70] Human hepatocytes also have immunogenicity issues. Besides impaired proliferative ability of hepatocytes as well as insufficient cell migration and limited space within the unhealthy liver also limit the use of human hepatocytes.[71]

Route of administration:

Route of administration is a major issue in stem cell therapy. Most preferred route of MSC administration is intravenous infusion. However, in different studies MSCs have been administered through hepatic artery, portal vein, intra-hepatic vein and intra-splenic vein.

The main aim remains to deliver transplanted stem cells to the hepatic sinusoids. Another frequently adapted route is the portal vein either by puncture of an intra-hepatic splenic vein tributary or an intra-hepatic portal vein tributary or an intra-hepatic portal shunt via jugular vein through hepatic venous system.[72, 73, 74]However, liver cirrhosis patients often have portal hypertension, which makes it difficult for transplanted cells to reach the hepatic sinusoids and usually all remaining cells get eliminated by macrophages with 24 hours. Besides, the portal vein is susceptible to embolism.[75]

While the hepatic arterial route has high rate of MSC colonization and survival, the peripheral venous route is straightforward and can be easily repeated.[76] However, the fourth i.e. intraperitoneal route should better be avoided, as it is associated with risks of secondary bacterial peritonitis, adhesion and interference with MSC migration.[77]

In our case, we injected GCSF to mobilize haemopoietic progenitor stem cells to the peripheral circulation from bone marrow. We use apheresis machine (COM.TEC, Fresenius Krabi AG, Hamburg, Germany) to collect enriched population of haemopoietic progenitor stem cells without any risk of contamination.[63,64] P1YA kit (Fresenius Krabi AG, Hamburg, Germany) was used to harvest haemopoietic progenitor stem cells from peripheral blood.[63,64] Number of haemopoietic progenitor stem cells was calculated by flow cytometry (Bacton Dickenson FACSVerse, Bacton Dickenson Biosciences, San Jose, CA, USA).[63] We administered haemopoietic progenitor stem cells through both hepatic arterial and iportal venous routes.[63,64]

Dose of administration:

Dose of MSCs remain a major issue for clinical application in liver disease. The usual dose of MSC in peripheral intravenous infusion is between $5x10^5$ to $1x10^6$ cells/kg.[78] Dose escalation study has shown that upto $2x10^8$ cells/time after 3 cycles of umbilical cord derived MSC infusion was safe in decompensated liver cirrhotics.[79]

Conclusion:

While stem cell therapy appears to be a safe and prospective treatment alternative for liver cirrhosis, there are still many gray areas that need to be answered like establishing a standard

treatment protocol, choice between MSC and human progenitor stem cell, route, dose and frequency of administration and in-depth appreciation of in vivo mechanism of action. Further interest and more randomized, multi-center clinical trials involving different liver diseases of different aetiologias will probably establish this promising modality as an effective one for the management of advanced liver diseases in the future.

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Author's Contribution:

MAM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
SMN, ALM, AR, MM, SMFA: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.