Could Stem Cell Therapy be the Cure in Liver Cirrhosis?

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Over the past five decades, liver cirrhosis has become an increasingly prevalent disease and one that will often require considerable medical intervention. However, current treatment options have demonstrated severe problems that have prompted research to provide a suitable alternative. These treatments are scarcely available, very expensive and present at a huge cost to the patient's quality of life. The introduction of stem cell therapy into liver disease has been heralded as the future of personalized medicine and may be the alternative that the healthcare system desperately seeks.

To truly determine the scientific basis surrounding this excitement, a literature search was carried out in January 2013 to determine all the data that was present in this topic area. All articles also underwent full cross-referencing to ensure no data was missed.

11 clinical trials were found to meet this criteria and trials were included in both English and non-English languages. The sporadic nature of the data across the trials, with various methods and stem cell types, made comparisons difficult.

The basic trends from the data were positive and the majority deemed the use of stem cells safe and feasible in patients presenting with cirrhotic liver disease. However, there is a clear requirement for more research, not only to determine the most efficacious technique and stem cell type but also to further understand stem cells to enhance progress. There may also be a requirement for a framework that future stem cell trials can be based on, which would allow future data to be comparative and allow valid conclusions to be drawn which may propel this therapy into standard clinical practice. (J Clin Exp Hepatol 2015;5:142–146)

In the past 50 years there has been a marked increase in the incidence and mortality of liver cirrhosis. As with any complex and advanced disease state, the incidence of severe associated complications has also risen. This has been attributed to an increase in alcohol abuse and non-alcoholic fatty liver disease in western culture and primarily be attributed to viral infection in eastern societies. Consequently, in 2011, liver cirrhosis accounted for over 33,500 deaths each year in the USA.[1] Liver cirrhosis is also a major risk factor for Hepatocellular Carcinoma, which accounted for 30,000 new cases with 22,000 deaths in USA in the past year.[2] The shocking nature of these figures shows the scale of the problem at hand and the requirement for a solution.

From a pathophysiological point of view, liver cirrhosis occurs as a progression of liver fibrosis, when the initial injury continues to persist.[3] Liver fibrosis is defined as the initial distortion of hepatic architecture. The accumulation of excessive collagen and extracellular matrix proteins is the primary cause of this change.[4]

Hepatocytes within a cirrhotic liver still have the ability to regenerate but this mismatch of regeneration and fibrosis is responsible for the clinical and biochemical dysfunction of the liver. It is questionable whether increasing the number of hepatocytes alone would have a positive benefit to the patients. This would not address the problem of the altered architecture and fibrotic tissue will still be present in vast quantities. A potential hypothesis is that a fully functioning compartment will be created through the proliferation of the infused stem cells allowing the return of liver function. This sounds promising to allow the medical community to consider pursuing this novel treatment option.

This review aims to highlight all current available evidence regarding the use of stem cell therapy in the treatment of liver cirrhosis and determine whether there is any factual basis for this excitement surrounding their potential.

CURRENT TREATMENT

Currently the only proven, effective and therefore recommended treatment of end stage liver disease is liver transplantation[5] which would require the donation of a healthy organ from either a living or cadaveric donor.

Keywords: liver cirrhosis, stem cell therapy, haematopoetic stem cells, mesenchymal stem cells, hepatic progenitor cells
Received: 3.1.2014; *Accepted:* 3.3.2014; *Available online:* 27.3.2014
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Abbreviations: HSC: Hematopoietic stem cell; MSC: Mesenchymal Stem cell; hHPC: Human Hepatic Progenitor cell; MNC: Mononuclear Stem cell; G-CSF: Granulocyte colony stimulating factor
http://dx.doi.org/10.1016/j.jceh.2014.03.042

This treatment option presents with its own set of problems; firstly, it is expensive[6] 'estimated at $150,000 or more during the first year following transplantation'. The most critical issue however is the marked shortage of donor organs available. This problem has been experienced globally and has led to high patient mortality.[7] Post-operatively, lifelong immunosuppression therapy is required to reduce the risk of rejection, compromising the patients' immune system. Long-term renal, cardiovascular and infective complications can occur as well as post-transplant lympho-proliferative diseases.[8] This expansive list of problems of the therapy highlights the advantageous nature of an alternative. The problems aren't just limited to the transplantation itself, as a knock on effect of the long waiting list and the critical condition of many patients, there may be a requirement for intensive supportive care and treatment to be maintained, either as palliative care or as bridging therapy to transplantation. These treatments come at a huge cost, not only to the health systems but also to the individuals.

With a niche in the market so blatantly visible, a surge in research is into alternative treatment for liver disease makes logical sense. The alternative treatment should not only be less invasive but also not generate the immune response commonly associated with transplantation.[9] To fully counteract the massive problems associated with current therapy, the requirement for the treatment to be readily available and economically affordable is one that must ideally be addressed. Hence, in theory, the use of stem cell therapy may be a viable future option and if fully harnessed could change the whole face of the treatment of liver disease.

STEM CELLS

Over the years of research, numerous types of stem cells have been identified. Each cell presents with a unique list o merits and capabilities but the disadvantages have been the main driving factor in determining the frequency of their use. As a broad entity, stem cells are defined as clonogenic undifferentiated cells, which cannot only self-renew indefinitely but can also differentiate into a variety of cell lineages.[10] These properties have raised excitement within the medical community, stem cells have been heralded as the future of personalized medicine and biological insurance for humans.

A stem cell's capabilities are mainly classified by their differentiative potential. Totipotent stem cells have the greatest range of differentiative capability, being able to transform into any cell type as well as forming the trophoblast.[11] However, it isn't possible nor necessary to extract a cell with such capabilities. Pluripotent stem cells are unable to form the trophoblast but are able to form any cell type from all three blastodermic layers[12] and these types of cells are available, if not commonly used. Multipotent stem cells are most commonly found in adult humans. However, their differentiative capabilities are limited to one germ line and are primarily used to replace damaged tissue within the human body.[8] The different types of stem cells that have currently been discovered for use are listed in Table 1.

As previously mentioned, the pitfalls of some of these stem cells is so severe that their use cannot be licensed and consequently only a handful of the stem cell types mentioned have been permitted for human use:

Hematopoietic stem cells (HSC) have been most routinely used in investigative stem cell therapy trials. While classically derived from bone marrow, it has been shown that these cells can be obtained from both umbilical and cytokine-mobilized blood.[9] These use of these cells is not a novel approach, they have been used in the treatment of blood disorders for almost three decades.[13]

Even though these cells are thought to be limited to cell lines within the hematopoietic system, the results of animal trials has highlighted their ability to differentiate into other lines, most relevantly into hepatocytes.[14–16] This strong pre-clinical evidence base has allowed the approval of these cells in cirrhotic patients.

Mesenchymal stem cells (MSC) are an alternative, multipotent, adult stem cell source that were initially derived from bone marrow stroma. As research progressed, menstrual blood and endometrium were found to be newer, potentially less invasive sources.[17] Russo and Parola[18] describe them as 'plate-adhering, fibroblast-like cells possessing self-renewal ability with the capacity to differentiate into multiple mesenchymal cell lineages'. To allow their use in liver disease patients, *in vitro* evidence has been presented showing the cells ability to differentiate into hepatocyte-resembling cells.[19]

Hepatic Progenitor cells (HPC) are found naturally and replicate specifically in the liver. However, the mechanism of this action is not fully understood[20] but it has been proven that the cell population increases proportionally to the severity of the disease progression.[21] Since these cells can be derived from human umbilical cord blood, its transplantation has been suggested as a treatment option to

Table 1 Different Types of Stem Cells and their Differentiation Potential.

Type of stem cell	Source	Differentiation potential
Embryonic	Human embryos	Pluripotent
Induced pluripotent	Reprogramming human somatic cells	Pluripotent
Hematopoietic	Bone marrow	Multipotent
Mesenchymal	Bone marrow	Multipotent
Hepatic progenitor	Human umbilical cord blood	Multipotent
Endothelial progenitor	Bone marrow	Multipotent