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Stem Cell Therapy for Patients with Chronic Liver Disease

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1. Introduction

Adult stem cells are a population of immature cells that have the capability of self renewal to provide the human body with a constant source of cells for maintaining healthy tissues or replacing those that are damaged. Our present day scientific developments alongside clinical experiences have collectively consolidated our understanding of the signals that mediate stem cell lineage commitment and differentiation. From this, the concept of using adult stem cells to repopulate chronically diseased organs is now a feasible option for regenerative medicine.

Whilst the use of human embryonic stem cells in the clinical setting has been overwhelmingly marred by its oncogenic potential as well as ethical concerns, the rate of progress in understanding the complex developmental plasticity of adult stem cells, in particular those derived from the bone marrow, has successfully allowed their use for translational research with unattached ethical issues. The pioneering use of bone marrow stem cells in the 1960s as a viable treatment option for leukaemia, myeloma and lymphoma has come a long way since then. Today we are able to use these stem cells to give rise to bone and cartilage (1) and to repair both cardiac and liver function (2, 3). Since a detailed review for each of these exciting developments is too broad for this chapter, we will mainly focus on the use of bone marrow derived stem cell for the treatment of chronic liver disease.

2. Chronic liver disease

Liver cirrhosis is the end stage of chronic liver disease and is associated with many serious systemic complications resulting from both liver failure and portal hypertension. This condition has a poor prognosis and is difficult to treat. In the UK alone as many as one in ten people have some form of liver disease where many die prematurely as a result (4). Liver disease is currently the fifth most common cause of mortality in the UK for both men and women and whilst the mortality rates for coronary heart disease, cancer, respiratory and cerebro-vascular diseases are falling, the death rates from all types of liver disease in England and Wales over the last 25 years showed over 150% increase in men and 100% in women (5). This significant upward trend clearly indicates a need to plan ahead for the health service. Worldwide, the common causes of liver fibrosis and cirrhosis include hepatitis B, hepatitis C and alcohol consumption. Other causes include immune mediated damage, genetic abnormalities, and non-alcoholic steatohepatitis which are mostly associated with diabetes and metabolic syndrome (6-8).

3. Cirrhosis

Liver cirrhosis or fibrosis is a common progressive pathological lesion of chronic liver disease that occurs in response to various liver-damaging factors. Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands which leads to portal hypertension; the development of hepatocellular carcinoma and end-stage liver disease. Over the past two decades the main cellular and molecular mechanisms of cirrhotic initiation and progression have been clearly defined. Various causative factors including hepatitis virus infection; ischemia; parasite infection; abnormal copper or iron load, all result in chronic inflammation which initially leads towards an excessive synthesis of the extracellular matrix (ECM). Activated hepatic stellate cells; injured or regenerated hepatocytes; Kupffer cells; sinusoidal cells and natural killer (NK) cells all produce cytokines and immunoreactive factors which exert various biological effects in an autocrine and paracrine manner to initiate fibrotic growth (9-12).

The detailed understanding of the natural history and pathophysiology of cirrhosis has resulted in better management of its complications to improve the quality of life of patients. Whilst pharmacological treatments can halt progression to decompensated cirrhosis, orthotopic liver transplantation (OLT) still remains the only highly successful and curative option for end stage cirrhosis. Survival data from the United Network of Organ Sharing (UNOS) study in 2004 indicated a survival rate of only 61% at 8 year post transplantation (13). OLT cannot be sustained as the only option for advanced liver failure. The limited availability of organs for a constantly growing list of patients requiring transplant in addition to issues of compatibility and comorbid factors means that not everyone is eligible for transplantation. There is therefore an unmet need to find a suitable alternative.

4. Hepatocyte transplantation

Hepatocyte transplantation has been identified as a promising alternative to OLT for certain liver-based metabolic disorders and acute liver failure. With the advantage of preserving the native liver, hepatocyte transplantation is less invasive and can be performed repeatedly to allow a higher chance for improved recovery in patients with acute liver failure (14-16). The mechanisms by which intraportally injected donor hepatocytes engraft into the host liver parenchyma involves cell migration within the liver sinusoids (17). These cells become trapped causing portal hypertension and ischemic-reperfusion (18, 19). This consequently initiates clearance by the innate immune system where the associated release of cytokines induces vascular permeability thus allowing surviving hepatocytes to translocate through the sinusoidal fenestrations and integrate into the liver parenchyma (20). Although the initial engraftment success of hepatocytes after transplantation is low, repeated hepatocyte transplantation in animal models have shown a sufficient increase in the number of engrafted cells to allow recovery from some metabolic defects (21). Isolation of hepatocytes is carried out from donor liver that are unused or not suitable for whole organ transplantation. Cells harvested from a single donor have the advantage of being used for multiple recipients in addition to being cryopreserved for use in emergency treatment of acute liver failure or for repeat treatment of liver-based metabolic disorders (22-24). To date hepatocyte transplantation has only been used to address single gene defects and some metabolic disorders where the risks associated with OLT are not justified or are aimed at avoiding or postponing liver transplantation. The most successful clinical outcomes of OLT have been in patients with metabolic disorders including those with urea cycle defects (23,

24); Crigler-Najjar syndrome type 1 (CN1) (25, 26); glycogen storage disease type 1 (27) and Factor VII deficiency (28). Although it was initially thought that transplantation of hepatocytes would be less immunogenic than whole organ transplantation, data from animal models demonstrated that the innate immune system clears a significant amount of hepatocyte irrespective of whether syngeneic or allogeneic cells are used (18). As a result most transplant facilities use the same immunosuppressive treatment as for liver transplantation (29). Since the clinical outcome following hepatocyte transplantation is still highly variable due to a multitude of factors including fibrotic damage to the liver which limits the proper engraftment of cells; the availability of the cells required to provide sufficient liver function over repeated infusion per patient, and often the very marginal quality of the cells isolated from donor liver, a new and readily available cell source must be identified. This strong demand has fuelled the interest in haematopoietic stem cells for treating acute liver failure.

5. The developmental plasticity of adult stem cells

It had previously been assumed that adult stem cells were lineage restricted, however the culmination of research over the past decade has now fully confirmed the remarkable developmental plasticity of human adult stem cells. The ability of adult bone marrow derived myogenic progenitors to participate in the regeneration of damaged skeletal muscle (30); ischemic myocardium (31-33); neurogenesis (34, 35) and the conversion of adult neural stem cells back into hematopoietic cells (36), redefined the biology of development. It was now accepted that the original three germ layers were not necessarily vital for transdifferentiation to occur (37). This implied that adult stem cells could exhibit similar pluripotency as embryonic stem cells.

6. Generation of hepatocytes by haematopoietic stem cells

The demonstration that adult bone marrow stem cells could differentiate towards a hepatic lineage was made almost a decade ago. Two independent research groups showed that the adult rat bone marrow contains a subpopulation of cells (about 3%) co-expressing the haematopoietic stem cell markers (CD34⁺, c-Kit, Thy-1); α -fetoprotein (AFP) and c-met. When they cultured this crude extract of bone marrow with hepatocyte growth factor (HGF) and epidermal growth factor (EGF), they were able to detect the expression of albumin, a marker of fully differentiated hepatocyte (38, 39). Over the years further refinement of the *in vitro* culture conditions led to the differentiation of haematopoietic cells that expressed more mature liver specific transcription factors including human Hepatocyte nuclear factor-1 α (HNF-1 α); cytokeratin (CK8); CK19 and AFP (40, 41). Studies on human adult bone marrow similarly confirmed their capability of differentiating into liver like cells (42, 43) where numerous cytokines and growth factors were shown to be important for driving this differentiation under *in vitro* conditions (44-46). More interestingly was the discovery that exposing rat haematopoietic stem cells to injured liver tissues induced the expression of functional hepatocyte factors (CK18, albumin and transferrin) (47). This suggested that the liver micro-environment alone was sufficient in providing the appropriate cues for inducing stem cell conversion towards the hepatic lineage. Several human post-mortem studies confirmed this observation where the presence of bone marrow derived cells were found in the liver. Theise *et al.*, (2000) investigated archival autopsy and biopsy liver specimens from recipients of sex-

mismatched therapeutic bone marrow transplantation and OLT (48). By immunohistochemical staining for CK8, CK18 and CK19, they identified hepatocytes and cholangiocytes of bone marrow origin as well as the detection of the Y-chromosome by fluorescent *in situ* hybridization (FISH). Using double staining analysis, they found a large number of engrafted hepatocytes (4%-43%) and cholangiocytes (4%-38%) - that were bone-marrow derived-replenishing the hepatic parenchyma. Despite a general variability of this observation amongst parallel studies (49, 50), the ultimate conclusion was that bone marrow derived haematopoietic stem cells were able to successfully engraft into the liver and gradually adopt a phenotype very similar to the hepatic lineage.

7. Human studies

Today, the most widely studied adult stem cells are derived from the hematopoietic lineage. Hematopoietic stem cells (HSCs) form part of the bone marrow compartment which constitutes a heterogeneous population of mesenchymal stem cells; committed progenitor cells and non-circulating stromal cells. The identification of HSCs from the bone marrow compartment is largely based on the expression of cell surface markers. Detecting the cluster of differentiation, CD34 is generally used in human studies as a surrogate marker for progenitor stem cells although there also exists a subpopulation of more primitive HSCs which do not express CD34 (51, 52). Despite the numerous studies that have shown bone marrow stem cells can give rise to hepatocytes, their use as a therapeutic agent is still in its infancy. Many studies are still at a pilot stage requiring randomisation and controls, however those reported show interesting results that require confirmation. The first clinical study was performed by a German group, am Esch *et al.*, (2005), where three patients were infused with autologous CD133⁺ cells subsequent to portal vein embolisation of right liver segments (3). A computerised tomography (CT) scan for volume analysis of the left lateral segments showed a 2.5 fold increase in growth rate of the three patients when compared to the control group without bone marrow stem cell administration. Despite the small number of patients and the lack of adequately sized randomised control group, this data showcased the promising potential of bone marrow derived stem cells in enhancing liver regeneration. A year later, a parallel study was reported by Gordon *et al.*, (2006) which included a phase I clinical trial on five patients with liver insufficiency (53). These patients were given granulocyte colony-stimulating factor (G-CSF) to mobilise their stem cells for collection by leukapheresis followed by purification of CD34⁺ expressing cells which were then injected into either the portal vein or hepatic artery. Three of the five patients showed improvement in serum bilirubin whereas four out of the five patients displayed significant increase in serum albumin. Clinically, the procedure was well tolerated with no observed procedure-related complications and the data concluded that there was a marked contribution of the stem cells towards regeneration of the damaged liver (53). In another independent study, Terai *et al.*, (2006) enrolled nine patients with liver cirrhosis where they were injected with autologously derived bone marrow stem cells enriched for the expression of CD34⁺, CD45⁺ and c-kit⁺. These patients were followed for 24 weeks where they showed a significant improvement in serum albumin levels in addition to significantly improved Child-Pugh scores (54). A year later, Rajkumar *et al.*, (2007) reported another small scale trial where 22 patients with chronic liver disease (Child-Pugh scores B-C) were enrolled (55). 200ml to 300ml of bone marrow aspirate were subjected to density gradient fractionation for isolation of CD34⁺ cells. These were then administered intravenously through the median cubital

vein. Liver function tests; ultrasound and CT scans were performed before, 4 weeks and 8 weeks following cell infusion. 32% of the patients showed a drop in bilirubin levels; 67% of the patients showed an increase in serum albumin levels and 73% showed reduction in ascites. No patients from this study showed severe adverse effects following transfusion and the overall quality of life index was significantly improved in the majority (82%) (55). In 2007, Mohamadnejad *et al.*, (56, 57) performed two clinical studies in patients with decompensated liver cirrhosis. In the first study they treated four patients each with 31.73×10^6 of cultured autologous mesenchymal stem cells, infused through a peripheral vein. The Phase I study demonstrated no side effects and the quality of life of all four patients improved by the end of follow-up. Furthermore, the model for end-stage liver disease scores of two patients (patient 1 & patient 4) showed marked amelioration in their Child Pugh scores by the end of follow-up. In the second study, they treated four patients with autologous CD34⁺ cells isolated from the bone marrow, which was slowly infused through the hepatic artery of the patients. In two patients they observed mild albumin improvement, however, the health of two patients further deteriorated where one died of liver failure a few days after the transplantation. This trial was prematurely stopped due to the severity of the side effects where it was concluded that infusion of CD34⁺ stem cells through the hepatic artery was not safe in decompensated cirrhosis, but suggested that it may be beneficial to use alternative routes to transplant CD34⁺ cells. Having corroborated the use of bone marrow stem cells as a regenerative therapy and demonstrated their safety in patients with liver insufficiency, Pai *et al.*, (2008) conducted a prospective clinical efficacy study of expanded adult CD34⁺ stem cells infused into the hepatic artery in nine patients with alcoholic liver cirrhosis (ALC) to determine whether clinical benefit was conferred (58). The primary end point was to assess the safety of infusing autologous stem cells into the hepatic artery of these patients; the secondary end point was to assess the improvement in liver function through serological and biochemical analysis; and to determine whether there were any symptomatic improvements. Following CD34⁺ stem cell infusion, CT scans showed normal enhancement in the liver parenchyma, with no evidence of focal liver lesions; additionally, duplex Doppler ultrasound scans showed normal flow in the portal veins and hepatic artery. To corroborate the safety and efficacy of improving liver function in patients with liver cirrhosis, Levicar *et al.*, (2008) then reported the results from a long-term follow-up (12-18 months) of patients with chronic liver disease injected with CD34⁺ enriched stem cells (59). During this time the patients were monitored for side effects, toxicity and changes in clinical, haematological and biochemical parameters. All the patients tolerated the treatment protocol without any complications or side effects related to the procedure. Four patients showed an initial improvement in serum bilirubin level, which was maintained for up to 6 months; whilst only a marginal increase in serum bilirubin was observed in three of the patients at 12 months. Only one patient showed an increase in serum bilirubin over slightly longer period of 18 months post-infusion. CT scans and serum AFP monitoring did not show any lesions or tumor formation in the patients. This successful study provided the basis for subsequent trials where more recently Li Nan *et al.*, (2010) reported the clinical outcome of autologous CD34⁺ infusion in patients with hepatitis induced liver failure (60). Twenty seven patients with Child- Pugh C cirrhosis were enrolled of which 22 were positive for Hepatitis B and 5 were positive for Hepatitis C. 50ml to 120ml of bone marrow aspirate were subjected to a Percoll gradient for the isolation of myeloid stem cells. 20 of the patients received cell infusion via the hepatic portal vein whilst 7 patients were infused via the hepatic artery using the Seldinger percutaneous technique. The patients were closely

monitored for 3 months following transplantation where it was initially noticed that liver function tests decreased for 3 days. The authors attributed this with the contrast media used to perform arteriography. Since all the patients had Child- Pugh C cirrhosis, the contrast media may have aggravated liver injury. Despite this, the patients did subsequently show an improvement in liver function by 1 week of transplantation. The most significant recovery was seen at 3 months post procedure where total bilirubin and albumin levels were highest. Overall, an improved clinical outcome was observed in the majority of the patients where jaundice was resolved and ascites improved 3 months after therapy. From this cohort of patients, two died, one due to peritoneal cavity infection and liver failure, and the second from a massive hemorrhage of the upper alimentary tract. The latest clinical study on patients with end stage liver disease has been reported by Nikeghbalian *et al.*, (2011) (61). Six patients were intraportally injected with autologous bone marrow-derived CD133⁺ cells. This arm of patients were compared with patients subjected short term infusion (6months) and long term infusion (12 months) of mononuclear cells. Liver function test was positive at 24 months of follow up in all the patients enrolled in this trial. Since there were no differences between the groups receiving MNC or CD133⁺ cell, this recent study has highlighted the versatility of bone marrow-derived progenitor mononuclear stem cells irrespective of the subpopulation of their cluster of differentiation markers. Furthermore this study also confirms their safe use to circumvent the need for liver transplantation in end stage liver disease.

The culmination of clinical trials thus far mentioned have shown a trend towards decreased serum fibrosis markers and improvements in bilirubin, albumin and Child-Pugh scores following stem cell infusion. The past decade has marked an important progress for regenerative liver therapy; however the accumulated data is still in its infancy. It is still not clear whether the route of infusion is important or whether mobilization of myeloid progenitor stem cells with G-CSF without leukapheresis is sufficient. Until more is learnt about the mechanisms by which HSCs contribute to hepatocyte regeneration, and the mechanism of clinical benefit in the recipient patients; controversy will inevitably shadow this form of treatment. Some authors have proposed that the observed conversion of infused stem cell to hepatocytes is simply a byproduct of cell fusion with no true induction of transdifferentiation (59, 60). Others have suggested that instead of adopting a new lineage, the stem cells indirectly serve a regenerative capability by stimulating activation of tissue specific stem cells and by inducing the release of vascular endothelial growth factor (VEGF) thereby increasing the blood supply to the cells and aiding in repair of the damaged tissue (61, 62). There are reports that also suggest HSCs may act in a regenerative capacity simply by inducing the expression of the B-Cell leukemia/lymphoma-2 gene (Bcl-2) and interleukin-6 (IL-6) in a paracrine manner thus suppressing apoptosis and inflammation of the surrounding tissue (62-64). In addition to these uncertainties, the homing mechanism of infused adult stem cells to the liver also remains unclear. There are suggestions that chemokines similar to stroma derived factor 1 may be involved, however, this remains to be validated (65). Although the application of stem cell therapy will not be prevented despite an incomplete understanding of the mechanisms involved, a clearer picture will ultimately enable better tailoring of stem cell therapy to the disease in question.

8. Current limitations

For cell replacement therapy is still too early to demonstrate its long-term effectiveness or its improvement in survival rate and in the quality of life. This will undoubtedly have to be

evaluated by more randomised control studies in the future. A standardised protocol will need to be established for the most efficient route of delivering infused HSCs; for the efficient long term culture of HSCs; for the optimal cell density and repeated transplantation required to re-establish liver function.

9. Future prospects

Autologous bone marrow infusion for patients with chronic liver disease has been shown to improve liver function parameters in contrast to observations accompanied by abstinence from alcohol. The degree of effectiveness of this therapy will likely to vary among different patients. Although the mechanisms underlining adult stem cell plasticity is still far from being fully characterised, the general enthusiasm regarding its potential clinical implication is heightened by the numerous clinical trials currently underway. In hepatology, the data presented here provides hope that human adult stem cells could eventually be used in tissue replacement protocols for the treatment of inherited and acquired end-stage liver diseases.

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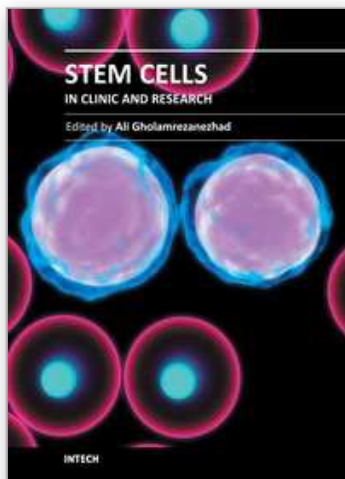
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Based on our current understanding of cell biology and strong supporting evidence from previous experiences, different types of human stem cell populations are capable of undergoing differentiation or trans-differentiation into functionally and biologically active cells for use in therapeutic purposes. So far, progress regarding the use of both in vitro and in vivo regenerative medicine models already offers hope for the application of different types of stem cells as a powerful new therapeutic option to treat different diseases that were previously considered to be untreatable. Remarkable achievements in cell biology resulting in the isolation and characterization of various stem cells and progenitor cells has increased the expectation for the development of a new approach to the treatment of genetic and developmental human diseases. Due to the fact that currently stem cells and umbilical cord banks are so strictly defined and available, it seems that this mission is investigational more practical than in the past. On the other hand, studies performed on stem cells, targeting their conversion into functionally mature tissue, are not necessarily seeking to result in the clinical application of the differentiated cells; In fact, still one of the important goals of these studies is to get acquainted with the natural process of development of mature cells from their immature progenitors during the embryonic period onwards, which can produce valuable results as knowledge of the developmental processes during embryogenesis. For example, the cellular and molecular mechanisms leading to mature and adult cells developmental abnormalities are relatively unknown. This lack of understanding stems from the lack of a good model system to study cell development and differentiation. Hence, the knowledge reached through these studies can prove to be a breakthrough in preventing developmental disorders. Meanwhile, many researchers conduct these studies to understand the molecular and cellular basis of cancer development. The fact that cancer is one of the leading causes of death throughout the world, highlights the importance of these researches in the fields of biology and medicine.

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