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Alternatives to Liver Transplantation in Pediatric Liver Diseases

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Abstract

Inherited metabolic disorders and acute liver failure (ALF) are often indications for liver transplantation in pediatric patients. Liver transplantation, however, is limited by the shortage of donor organs, as well as by the need for chronic immunosuppression. This review focuses on the latest advancements made in the field of liver regenerative medicine as possible future alternatives to pediatric liver transplantation or as a means of temporary liver function support. Cell transplantation offers great promise for the treatment and long-term correction of inherited metabolic disorders, especially when *ex vivo* gene therapy is combined with autologous hepatocyte or induced pluripotent stem cell (iPSC)-derived hepatocyte-like cell (HLC) transplant. Bioartificial liver (BAL) systems are currently being tested that may be able to bridge patients to either liver transplantation or endogenous liver regeneration, in the case of ALF. Still, further research is required before these forms of cell therapy are incorporated into clinical practice: the optimal cell type for both cell transplantation and BAL systems must be found, methods for the large-scale expansion of these cells must be created, and safety concerns pertaining to each cell type must be addressed.

Introduction

Liver transplantation is to date the only proven treatment for pediatric end-stage liver diseases, including biliary atresia and other cholestatic diseases, as well as acute liver failure (ALF) and a number of inherited metabolic disorders [1]. Although the success of this operation has improved significantly in the past few decades, and the scarcity of organs has been to some extent circumvented by the utilization of split-liver grafts and living-related donors [2], it requires life-long immunosuppression, with the medical complications and growth restrictions that this entails [3]. Alternatives to liver transplantation are actively being sought after, and cell therapy has shown promise for the treatment of both inherited metabolic disorders and acute liver failure.

Inherited metabolic disorders

Metabolic disorders are the second most common indication for pediatric liver transplantation after biliary atresia [4]. They can be divided into 1) diseases that result in structural liver damage with liver failure or cirrhosis, such as α1-antitrypsin deficiency, and 2) diseases that are due to an enzymatic defect expressed solely or predominantly in the liver, but that result in injury of other organ systems, such as Crigler-Najjar type 1 syndrome [5]. In these diseases cell transplantation offers the potential for long-term correction of the metabolic deficiency [6].

Furthermore, primary hepatocyte or stem cell-derived hepatocyte-like cell (HLC) transplantation, delivered into the liver via the portal vein, is less invasive than orthotopic liver transplantation, and as the native liver is not removed the transplanted cells need not replace all hepatic functions, but only improve the single enzyme deficiency [7]. For the treatment of metabolic disorders, cell transplantation aims at the addition of cells rather than at the replacement of diseased cells.

Primary hepatocyte transplantation has been used to treat a number of metabolic disorders in both adults and children, including familial hypercholesterolemia, Crigler-Najjar syndrome type 1 (CNS1), urea cycle defects (UCD), infantile Refsum disease, glycogen storage disease type Ia, and progressive familial intrahepatic cholestasis, with clinical improvement and partial correction of the metabolic abnormality in most cases [8]. In children, most experience in liver cell transplantation has been acquired in the treatment of CNS 1 and UCD [9]. The success of hepatocyte transplantation in CNS 1 is easily monitored through reduction of plasma bilirubin [10], and its beneficial effects have been reported to last up to 11 months [11]. Management of hyperbilirubinemia in a CNS 1 infant patient was also achieved through transplantation of hepatic progenitor cells [12]. In UCD, periods of hyperammonemia and clinically relevant crises were shown to be reduced during an observation period of up to 13 months [13]. Individual results are encouraging, but controlled clinical trials are necessary to evaluate the overall significance of hepatocyte transplantation for the treatment of metabolic diseases [14]. Furthermore, with allogeneic hepatocyte transplantation the issues inherent to rejection and immunosuppression remain [15], and its use is limited by the available supply of liver tissue [16]. Autologous hepatocytes can also be used, but this involves performing a liver resection.

An alternative is the production of autologous stem cell-derived HLCs. With the development of stem cell technology, and especially human induced pluripotent stem cells (hiPSCs), the treatment of hereditary liver disease can be taken a step further: patient-specific therapies can be created by combining genetic correction with autologous cell transplantation [17,18]. This allows for the bypassing of the two main issues inherent to treatment with embryonic stem cells (ESCs): ethical concerns raised by the destruction of embryos, and the possibility of immune incompatibility. Disease-free autologous hiPSCs are generated through *ex vivo* gene therapy [19], and the genetically-corrected hiPSCs may then be differentiated and used for

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transplantation. A patient-specific, disease-free line of hiPSCs can be obtained in 4-5 months [20]. To date, α1-antitrypsin deficiency and familial hypercholesterolemia have both been genetically corrected in hiPSCs [21,22]. This can also be done using autologous hepatocytes, but as discussed earlier these must be obtained through liver resection. Clinically, successful *ex vivo* gene therapy and autologous hepatocyte transplantation has been performed only once, for familial hypercholesterolemia [23]. More recently, a combination of *ex vivo* gene therapy with a lentiviral vector encoding FAH and autologous hepatocyte transplantation was used to correct hereditary tyrosinemia type 1 in an FAH-deficient pig model [24]. In contrast to hepatocyte transplantation [25], there are no established large animal models of human metabolic disease treated successfully with stem cell-derived HLCs [26].

Genetically-corrected autologous hepatocyte or stem cell-derived HLC transplantation may be the logical next step in the treatment of inborn errors of metabolism. However, several important limitations to widespread clinical use of cell transplantation for correction of metabolic deficiencies still exist. Results, although promising, are still modest, and evidence of long-term efficacy is lacking. This may in part be due to the low levels of engraftment seen in cell transplantation. Some diseases, such as hereditary tyrosinemia type I and α1-antitrypsin deficiency,inherently provide a natural selective advantage for the transplanted cells [27,28], but in other cases injury to the recipient liver or other methods to increase engraftment may be necessary [29,30]. Furthermore, and although cell transplantation is far less invasive than orthotopic liver transplantation, it has on rare occasion been associated with complications including portal vein thrombosis [31,32]. Finally, there are other limitations to cell therapy that are specific to the use of stem cells particularly: stem cell-derived HLCs have not yet reached a full degree of functional maturity, and the issue of their potential for tumorigenicity must be addressed [33].

Cell transplantation may in the future take the place of liver transplantation for the treatment of inherited metabolic disorders in children. Before this happens, however, the ideal cell type for this therapy must be identified, and a method for efficient, large-scale production of cells, as well as for their successful engraftment after transplantation, must be developed. More information is necessary on the dosage of cells required in children, taking into account that restoration of around 10% of original enzyme activity is usually sufficient to achieve metabolic control [34], and on the optimal method of delivery [35]. Further research on the use and behavior of stem cell-derived HLCs is also necessary in order for them to be safely incorporated into clinical practice. These advancements may beused not only for inborn errors of metabolism, but also for the treatment of hepatocellular carcinoma and chronic liver disease in adults [36]. In the case of inherited metabolic disorders specifically, *ex vivo* gene therapy followed by autologous cell transplantation holds great promise for the treatment of single-gene abnormalities.

Acute liver failure

ALF is an emergent situation with high mortality rates and a very limited time frame to locate and prepare a donor liver suitable for transplantation [37]. In this context, cell therapy may serve as a bridge to liver transplantation by supporting hepatic function while waiting for a donor organ [38]. This may be achieved through two methods: liver cell transplantation or bioartificial liver (BAL) support systems. Liver cell transplantation has been reported in at least ten pediatric patients, with hyperammonemia reduction, coagulation improvement, and hepatic encephalopathy regression seen in the majority of patients [9].

BAL systems remove toxic substances from the blood through albumin dialysis and at the same time perform synthetic liver functions through the incorporation of live, functioning hepatocytes into the device [39]. To date, none of the tested BAL devices have demonstrated survival benefit in a randomized controlled trial despite improvement in clinical and biochemical parameters [40,41], but research in this field is still very active, with a spheroid reservoir BAL recently being shown to improve survival in a porcine model of drug-overdose ALF [42]. Porcine hepatocyte spheroids have also been used in a BAL built for pediatric use and have displayed successful ammonia detoxification [43], but this device has not been clinically tested. Further investigation of BAL systems in the clinical and pediatric settings is warranted.

Several different cell types have been tested in BAL devices; to date, none has demonstrated clear superiority over the others. Primary hepatocytes show a tendency to lose function and apoptose *in vitro*, which may be partially overcome by culture in a spheroid configuration [44], but human hepatocytes are not easily accessible and porcine hepatocytes used in the HepatAssist device are associated with concerns of xenozoonosis. HepG2/C3A immortalized hepatoblastoma-derived human cells have also been used in the ELAD device, but the issue of their possible tumorigenesis has not yet been resolved. A future solution to this problem may be the expansion of hepatocytes in large-scale animal bioreactors: animal models of tyrosinemia type 1 have been created that could allow for liver repopulation with human hepatocytes due to the graft's selective advantage over the native fumarylacetoacetate (FAH)-deficient cells [45,46]. Finally, hepatocytic induction of fibroblasts into hiHeps has recently yielded promising results in a BAL device demonstrating improved survival in a porcine ALF model [47].

Although liver transplantation is the only proven therapy for patients unlikely to recover from ALF, a large retrospective United Network for Organ Sharing (UNOS) data analysis showed that 5-year patient and graft survivals in children with ALF were significantly lower than in children transplanted for biliary atresia [48]. Furthermore, recovery without transplantation occurs in 15%-20% of patients with severe hepatic encephalopathy [1]. This means that endogenous regeneration takes place in the liver that in some cases is capable of restoring hepatic function, so that cell therapy may be able to eliminate the need for liver transplantation in selected patients [49]. When transplantation is necessary, bioengineered liver grafts may in the future allow us to bypass the shortage of donor organs while eliminating the need for chronic immunosuppression [50,51].

Conclusions

Cell therapy has shown promise as an alternative to orthotopic liver transplantation for the treatment of inherited metabolic disorders and ALF in pediatric patients. Primary hepatocyte transplantation has been used in children with CNS 1 and UCD with encouraging results, and in the future genetically corrected autologous stem cell-derived HLC transplantation may offer a long-term solution to single-gene metabolic disorders. In both metabolic disorders and ALF, cell therapy may serve as a bridge to liver transplantation by supporting normal liver function while a suitable donor organ is found, and in ALF cell-based therapeutics may in some cases also serve as a bridge to spontaneous endogenous regeneration, bypassing the need for liver transplantation altogether. Cell therapy for ALF includes cell transplantation as well as BAL systems. However, several important challenges must be overcome before these practices are incorporated into the clinical setting. Namely, the optimal cell type for each modality of cell therapy must be determined, and mechanisms set in place for the obtainment of cell quantities sufficient for large-scale clinical application, with efficient *in vitro* culture and in cell transplantation successful *in vivo* engraftment. Furthermore, these treatments must demonstrate safety in humans and within the framework of pediatrics.

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