LIVER DISEASE

INTRODUCTION

There are several types of liver disease that may potentially be treated by cell-based therapies including metabolic liver diseases, acute liver failure, and chronic liver disease. The metabolic liver diseases include the various genetic diseases of liver metabolism predominantly affecting the hepatocyte. Acute liver disease due to toxins, viral infection etc. causes widespread death of liver cells and if severe leads to the rapid deterioration in the patients clinical condition and even death. Chronic liver disease, due to multiple causes including obesity, alcohol, viral infections, immune diseases etc., can cause chronic scarring of the liver and reduce the liver's function leading to cirrhosis, ultimately causing liver failure. For severe and end stage liver disease the current gold standard of care is whole liver transplantation, however this is limited by the negative side effects of immunosuppression and organ availability. The development of cell therapies has therefore been an attractive option.

RATIONALE AND EXPERIMENTAL EVIDENCE FOR CELL-BASED THERAPIES FOR LIVER DISEASE

In the context of genetically-based metabolic liver disease, the functional replacement of diseased hepatocytes with hepatocytes that contain the corrected gene may be sufficient to have clinical benefit. Examples of diseases where this may be possible include Tyrosinemia type 1 (due to fumarylacetoacetate hydrolase deficiency), and Crigler–Najjar syndrome type I (which causes hyperbilirubinaemia). While acute liver failure might be complicated by the development of multi-organ failure which would require distinct management, the replacement of healthy hepatocytes may also be sufficient to treat the disease effectively. For chronic liver disease, and its end-stage manifestation of cirrhosis, the situation is more complex as the simple replacement of hepatocytes may not be adequate to correct disease. This is because the degree of scarring and inflammation may prevent the transplanted cells from surviving and integrating effectively. For liver cirrhosis it may therefore be necessary to develop therapies which target the scarring and inflammation as well as replacing or supplementing the damaged hepatocytes or biliary cells.

WHAT IS THE CLINICAL STATUS OF CELL-BASED THERAPIES FOR LIVER DISEASE?

There have been several cell-based clinical studies for liver disease of various types including acute and metabolic liver disease as well as liver cirrhosis. There have been encouraging clinical results from hepatocyte transplantation for a variety of metabolic liver diseases such as Crigler Najjar, glycogen storage disease type 1, and Urea cycle disorders (Iansante et al.). Hepatocyte supply is a challenge and new sources of hepatocytes would have an impact in this area. Currently, for liver cirrhosis there is no clear evidence that cell therapy works. There have been a number of small studies that have shown some possible benefit but larger randomised controlled trials have so far failed to show positive outcomes (Moore et al., Newsome et al.). As such, treating cirrhosis with cell therapies cannot be recommended outside of properly funded clinical trials.

WHAT DOES THE NEAR FUTURE HOLD?

There have been encouraging results from studies that have sought to grow liver cells in the laboratory from various sources including pluripotent stem cells and adult stem cells taken from normal human livers. Recent studies have suggested that human hepatocytes and biliary cells can be expanded as organoids which may potentially allow them to be used as cell therapies to treat metabolic and acute liver disease (Hu et al.), and as a cell source for treating biliary disease (Huch et al.).

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Stuart Forbes, MD, PhD, University of Edinburgh, MRC Centre for Regenerative Medicine, and the ISSCR Clinical Translation Committee

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