Clinical-grade human liver mesenchymal stem cells for the treatment of NASH-Fibrosis through immunomodulation

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Introduction

Material & Methods

Cell identity & Characterization

A full HepaStem gene expression profile analysis was done to evaluate the cell’s identity and compared to hepatocytes. In production, each batch is quality controlled on its mesenchymal identity (flow cytometric analysis of CD73 and CD90) and its identity (CD45/CD31/CD133/CD193). The immunomodulatory profile, as well as inflammatory conditions was analyzed using flow cytometry (HLA-ABC, HLA-DR and HLA-G). The HGF secretion profile of immunomodulatory cytokines by HepaStem was also evaluated with and without the addition of inflammatory cytokines (IL1, TNFa, IFNg and TNFa).

Cell in vitro Immunomodulatory Functionality

The anti-inflammatory effect of HepaStem was investigated towards T-lymphocytes and dendritic cells. In co-culture systems with CellTak™-treated T-cells, HepaStem cytokines were stimulated by DCs in a mixed leucocyte reaction using different HepaStem/T-cell ratios. The percentage of proliferation of the responding T cells was assessed by flow cytometry by the analysis of the CSFE profile.

Results

Cell in vivo effect on fibrotic collagen deposition in a NASH mouse model

As a living medicinal product, HepaStem is proposed to treat NASH by decreasing the exaggerated systemic and liver inflammation through the restoration of an immune balance, in a responsive way using multiple modes of actions. A single HepaStem injection significantly decreased the NAS score, which was mainly attributed to reduction in inflammation and the fibrosis will be reduced as a consequence, furthermore HepaStem have been shown to secrete HGF, which inhibits the proliferation and collagen deposition by adult liver progenitor cells. In addition to the systemic action, MSCs could have a major tropism for the liver where it could have local immunomodulatory effects and to a second extent an ability to secrete growth factors aiding to reduce liver functionality. Through liver tissue regeneration, fibrosis can be degraded and restricted which will lead to a diminishing of fibrosis in case there is no new fibrosis formation as the inflammation and fibrosis formation is inhibited by HepaStem.

Discussion

The proposed mechanism of action of HepaStem in NASH is a systemic inhibition of inflammation and inhibition of defective cell activation. The effect works through the secretion of several cytokines (HGF, IFNγ, PGE2) in response to the liver inflammation. HGF has previously been shown to be involved in the inhibition of hepatic stellate cell proliferation and collagen deposition by adult liver progenitor cells.

Conclusion

The preclinical results suggest that clinical grade liver progenitor cells have anti-inflammatory anti-fibrosis and anti-BNFF effects, both in vitro and in an NASH mouse model. As these cells are GMP manufactured, and cryopreserved as easy to use, off-the-shelf, easy to bring to the bed-side product, which have shown safety/tolerability in a Phase I/II study treating metabolic disorders, this cell therapy is now ready for a first clinical trial in NASH/fibrosis patients.