ORIGINAL ARTICLE

Phase 1–2 pilot clinical trial in patients with decompensated liver cirrhosis treated with bone marrow–derived endothelial progenitor cells

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The aim of this nonrandomized, open label, phase 1 clinical trial was to evaluate the safety and the feasibility of the treatment with autologous bone marrow–derived endothelial progenitor cells (EPC) in decompensated liver cirrhosis. In addition, the changes in liver function and hepatic venous pressure gradient (HVPG) and their relation with the characteristics of the cellular product were analyzed. Twelve patients with Child-Pugh ≥8 liver cirrhosis underwent bone marrow harvest for *ex vivo* differentiation of EPC. The final product was administered through the hepatic artery in a single administration. Patients underwent clinical and radiologic follow-up for 12 months. The phenotype and the ability to produce cytokines and growth factors of the final cellular suspension were analyzed. Eleven patients were treated (feasibility 91%). No treatment-related severe adverse events were observed as consequence of any study procedure or treatment. Model for end-stage liver disease score improved significantly (*P*0.042) in the first 90 days after cells administration and 5 of the 9 patients alive at 90 days showed a decreased of HVPG. There was a direct correlation between the expression of acetylated-low density lipoprotein and von Willebrand factor in the cellular product and the improvement in liver function and HVPG. The treatment with EPCs in patients with decompensated liver cirrhosis is safe and feasible and might have therapeutic potential. Patients receiving a higher amount of functionally active EPC showed an improvement of liver function and portal hypertension suggesting that the potential usefulness of these cells for the treatment of liver cirrhosis deserves further evaluation. (Translational Research 2016;■:1–12)

Abbreviations: EPC = endothelial progenitor cells; VEGFR = vascular endothelial growth factor receptor; vWF = von Willebrand Factor; acLDL = Acetylated-low density lipoprotein; CXCR4 = C-X-C chemokine receptor type 4; VEGF = vascular endothelial growth factor; EGF =

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epidermal growth factor; HGF = Hepatocyte growth factor; IGF = insulin like growth factor; CT-1 = Cardiotrophin-1; IL-6 = Interleukine 6; SDF = stromal cell-derived factor; HVPG = Hepatic Vein Pressure Gradient; ICG = indocyanine green clearance

AT A GLANCE COMMENTARY

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Background

In the experimental setting, endothelial progenitor cells (EPC) have been regarded as a potential treatment for liver cirrhosis, but no clinical studies have investigated the safety and the feasibility of the treatment with autologous EPC in this setting.

Translational Significance

In this pilot clinical trial, bone marrow–derived EPC were administered through the hepatic artery in patients with decompensated cirrhosis. The treatment was feasible and safe, and the results suggest that EPC administration might be beneficial for liver function and portal hypertension as bridging therapy, whereas waiting for liver transplantation or as supportive therapy for patients not eligible for transplantation.

INTRODUCTION

End-stage liver cirrhosis is the main indication for liver transplantation in Europe and the ultrasound (US).[1,2] Regrettably, many patients awaiting transplantation are not transplanted due to high mortality and dropout rates while in long waiting lists as result of organ shortage.[2] Moreover, a significant amount of patients are not suitable for transplantation for different reasons, mainly comorbidities or advanced age. In absence of liver transplantation 1-year mortality rate among patients with decompensated liver cirrhosis is very high, ranging from 20% to 55% in Child-Pugh score B and C, respectively.[3,4] In the setting of end-stage liver cirrhosis, regenerative therapies could help in bridging patients for transplantation and improving the quality of life of those patients that are not eligible for the intervention. Bone marrow progenitor cells have been advocated as a potential therapeutic tool for different types of liver disease.[5-8] In the last 15 years, transplantation of different bone marrow progenitors has proved beneficial in animal models of acute and chronic liver diseases.[8-10] In patients with chronic liver disease, the administration of bone marrow progenitors by different routes was also shown to provide therapeutic benefit.[10-15] However, studies are very heterogeneous regarding design, characteristics of patients, cells used, and administration route, so no definitive conclusions can be drawn regarding the safety and the efficacy of this treatment. Recently, endothelial progenitor cells (EPC), a subtype of bone marrow progenitors, showed hepatoprotective activity in experimental models of liver injury.[16-19] EPC represent a small percentage of bone marrow progenitors and can be detected in the bloodstream at a very low concentration. EPC are recruited to damaged tissues and seem to contribute to tissue regeneration, especially through their ability to release cytoprotective factors[9,20] and to stimulate vasculogenesis and neoangiogenesis.[21,22] Experimental data suggest that during liver damage these cells produce cytokines and growth factors that promote scar tissue degradation and hepatocyte proliferation.[23] EPC were characterized for the first time in 1997,[21] but we still lack a universal agreement on the phenotype criteria that should be used for their identification.[24] Yet, there is a general agreement that 2 different populations of EPC can be identified, late and early EPC.[22,25,26] These 2 cell subsets exhibit different expression of progenitor cell markers (CD133) and endothelial markers (vascular endothelial growth factor receptor [VEGF-R] 1 and -2); however, they show a similar vasculogenic ability. Compared with early EPC, late EPC show lower expression of progenitor markers (CD133 and CD 34), whereas the expression of vascular endothelial growth factor receptor (VEGFR)-1 and VEGFR-2 is higher. The expression of the common leukocyte antigen (CD45) gradually decreases from mononuclear cells to late EPC.[22] In culture, they are typically recognized by their spindle-shaped aspect and by their ability to form tubes. The capacity for uptaking acLDL and binding Ulex-lectin constitute 2 major functional markers of these cells.[21] Although experimental studies suggest that EPC may revert liver fibrosis and improve the prognosis of liver diseases,[16-18] there is no clinical support to the use of EPC in the treatment of patients with liver cirrhosis. Furthermore, there is no evidence that EPC for therapeutical use can be obtained from the bone marrow of cirrhotic patients.

Therefore, the main aim of this phase 1–2 trial was to evaluate the feasibility and safety of the administration of autologous bone marrow–derived EPC in patients with liver cirrhosis. Their effect on liver function and portal hypertension was also assessed as a secondary aim.