STIFTUNG FÜR LEBERKRANKHEITEN

Universitätsklinik für Viszerale Chirurgie und Medizin
Hepatologie

Research Progress Report:
Comparing the intrahepatic effects of carvedilol and simvastatin in experimental liver cirrhosis

Name of Grantee: Yeldos Nulan
Date: 08/05/2026

Summary / Brief outline of topic
Portal hypertension (PH) arises primarily due to increased intrahepatic vascular resistance (IHVR) driven by structural alterations, such as architectural remodeling due to hepatic stellate cells (HSCs) activation, and elevated hepatic vascular tone resulting from liver sinusoidal endothelial cells (LSECs) dysfunction.Non-selective-beta-blockers (NSBBs) lower PH through extrahepatic actions. Recently, in experimental cirrhosis, we found that carvedilol, a newer generation NSBB with additional anti-alpha1- adrenergic activity, achieves a superior reduction in portal pressure (PP) compared to traditional NSBBs by decreasing IHVR (PMID: 41659769). Simvastatin, a type of HMG-CoA reductase inhibitor, is well established in reducing IHVR by 1) improving LSECs phenotype and increasing NO release, and 2) deactivating HSCs, both through the Krüppel-like factor 2 (KLF2) transcription pathway. Building on the findings regarding carvedilol clarified before, the present study aims to compare and evaluate the potential synergistic effects of carvedilol and simvastatin in reducing HSCs and LSECs activation and dysfunction both in vitro and in vivo in a rat model of cirrhosis.

Activities
In vitro: LSECs and HSCs were isolated from cirrhotic rats (i.p.thioacetamide 12 weeks) and then cultured with carvedilol (C) / simvastatin (S) / carvedilol plus simvastatin (C+S) for 24 hours. Endothelial function was assayed by NO bioavailability. Cell contraction assays were performed in cirrhotic HSCs. (n=3-5)

In vivo: hepatic hemodynamics were assessed in cirrhotic rats treated with carvedilol (10mg/kg/day) or simvastatin (25mg/kg/day) or carvedilol plus simvastatin for 2 weeks (n=6-9). Hepatic remodeling was evaluated by measuring the collagen proportionate area (CPA), and HSCs activation were assessed via immunofluorescence detection of alpha-smooth muscle actin (α-SMA) in liver sections

Results
In vitro: NO release was increased in all experimental groups vs vehicle, by 2.2, 2.3 and 2.2 fold-change respectively. HSCs cell contraction was reduced by 49% in C ,78% in S, and 84% in C+S.
In vivo: All treatments reduced PP by 29.7% (C), 16.9% (S), and 29.5% (C+S). CPA-positive area in liver tissue slides was reduced by 35.1%, 35.0% and 26.4% respectively. αSMA-positive area was reduced by 33.5%, 32.7%, and 32.5% respectively (all $p < 0.05$).

Administration: Lilian Smith
Murtenstrasse 35, 3008 Bern, Tel. +41 31 632 32 88
info@swissliver.ch
www.swissliver.ch

Discussion
These results indicate that combined carvedilol and simvastatin treatment is comparable to their individual effects in the current animal models and at this disease stage. Whether carvedilol and simvastatin exert synergistic effects may be evaluated in more advanced stages of cirrhosis or in alternative disease models.

Achievements (Grants / Prizes / Publications)
Nulan Y, Felli E, Selicean SE, Prampolini M, Berzigotti A, Gracia-Sancho J, Bosch J. Carvedilol decreases hepatic vascular resistance by reducing fibrogenesis and reversing endothelial dysfunction in cirrhotic rats. JHEP Rep. 2025 Nov 20;8(3):101681. doi: 10.1016/j.jhepr.2025.101681. PMID: 41659769; PMCID: PMC12878606.

Abstract is accepted for EASL 2026 Poster
Abstract Title: Comparing the intrahepatic effects of carvedilol and simvastatin in experimental liver cirrhosis
Abstract Number: REG26-586

Outlook / Next steps
In the present study, we observed that carvedilol and simvastatin exert comparable effects, both when administered individually and in combination, on intrahepatic remodeling. These effects include improvement of liver sinusoidal endothelial cell (LSEC) function and reduction of hepatic stellate cell (HSC) activation. However, under the experimental conditions tested, we did not detect a synergistic effect of combined carvedilol and simvastatin treatment. This may be attributable to the specific disease model and stage (thioacetamide (TAA)–induced cirrhosis after 12 weeks i.p injections).

Chronic liver disease comprises heterogeneous etiologies, including alcohol-associated liver disease (ALD), metabolic dysfunction–associated steatohepatitis (MASH), and autoimmune liver diseases, each characterized by distinct pathogenic mechanisms. Therefore, future studies we may incorporate etiology-specific disease models. Integrating different etiologic models into the experimental design, rather than relying solely on TAA-induced cirrhosis, may allow a more comprehensive evaluation of treatment effects and potential drug synergistic effects.

Administration: Lilian Smith
Murtenstrasse 35, 3008 Bern, Tel. +41 31 632 32 88
info@swissliver.ch
www.swissliver.ch