In vivo MTD study of new potential inhibitors of Proprotein Convertase Subtilisin/Kexin 9 (PCSK9)

Beatrice Mattina[1], Marcella Palumbo[1], Paola Bonicco[1], Lisa Giannessi[1], Federica Vacondio[1], Nicola Ferri[2], Francesca Zimetti[1], Francesco Potì[1], Marco Radi[1], Ilaria Zanotti[1]

[1] Department of Food and Drug, University of Parma, Italy
[2] Department of Medicine, University of Padua, Italy
https://doi.org/10.56095/eaj.v4i1.96
Beatrice Mattina: beatrice.mattina@unipr.it

Aim: This study aims to determine the *in vivo* safety of newly synthesized PCSK9 inhibitors (MR-compounds). PCSK9 controls peripheral and central cholesterol levels and it plays a crucial role in hypercholesterolemia, being a well-established pharmacological target to treat this pathology, while a possible involvement in the aetiopathogenesis of AD has been postulated. Currently, the available PCSK9i to counteract hypercholesterolemia are very expensive biotechnological drugs and only subcutaneously administrated. Based on these premises, orally bioavailable small-molecules may be a valuable addition to existing treatments.
Methods: After preliminary *in vitro* screening in human hepatocyte and neuroblastoma cells of 30 compounds, 4 compounds were selected to test tolerability and bioavailability *in vivo* in wild-type mice (C57BL/6J) at 12.5mg/kg, 25mg/kg, 50mg/kg, and 100mg/kg for 5 days. MR-532 and MR-533 were administered subcutaneously, while MR-3 and MR-644 both subcutaneously and orally. Body weight and phenotype analysis were assessed daily to evaluate tolerability and macroscopic toxicity. After the sacrifice, hepatic toxicity (histological analysis and ALT activity) and biodistribution (LC-MS/MS) were evaluated.
Results: All doses of compounds were well tolerated (no changes in body weight, food intake, coat; no lethargy was observed). The MR-532 and MR-533 at 100mg/kg did not show elevated levels of ALT activity compared to vehicle (66mU±55, 76mU±127, and 130mU±203, respectively) or inflammatory cell infiltration or necrosis in liver sections (histological analysis). Interestingly, MR-532 and MR-533 were detected at all doses in plasma (261-318nM; 159-192nM), liver (522-1063pmol/g; 2824-3135mol/g) and brain (513-779pmol/g; 457-380mol/g), respectively, without a dose-dependent trend. MR-3 and MR-644 analyses are in progress.
Conclusion: All tested compounds proved to be safe. MR-532 and MR-533 showed plasma and hepatic bioavailability. They can reach the CNS, although at low concentrations. Further investigations are needed to understand how the route of administration affects biodistribution and to evaluate the efficacy of these compounds in cardiovascular and neurodegenerative diseases.

Clinical outcomes of early post-discharge cardio-geriatric ambulatory care in frail patients after acute heart failure. A controlled before-and-after study

Chukwuma Okoye[1,2,3], Tessa Mazzarone[4], Alberto Finazzi[1], Daniela Guarino[4], Adriana Antonella Bruni[2], Lorenzo Maccioni [4], Giulia Pescatore[4], Maria Giovanna Bianco[4], Cinzia Guerrini[4], Andrea Giusti[4], Giuseppe Bellelli[1,2], Agostino Virdis[4]

[1] School of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy
[2] Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
[3] Department of Neurobiology, Care Sciences and Society, Department of Geriatrics Aging Research Center, Karolinska Institutet and Stockholm University, Stockholm, Sweden
[4] Geriatrics Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy
https://doi.org/10.56095/eaj.v4i1.97
Tessa Mazzarone: tessa.mazzarone@phd.unipi.it

Aim: To assess whether an early post-discharge Cardio-Geriatric (CG) outpatient service reduces 1-year mortality compared to usual care (UC), and to evaluate 1-year rehospitalization rates and days alive and out of hospital (DAOH).
Methods: In this single-center, controlled before-and-after study, patients aged ≥75 years hospitalized for acute HF were included. In the UC group, patients discharged between January 2018 and December 2019 received standard follow-up with referrals to a cardiologist and general practitioner. In the CG group, patients discharged between January 2020 and December 2022 attended a Cardio-Geriatric ambulatory care within three weeks of discharge. Primary outcomes were one-year all-cause mortality, heart failure readmissions, and days out of hospital (DOAH). The effectiveness of CG follow-up was assessed using a 1:1 propensity score matched (PSM) analysis.
Results: A total of 652 patients (mean age 86 years, 56% female) were included in the study, with 477 receiving UC and 175 referred to CG follow-up. After propensity score matching of 350 patients (50% CG), we observed a significant reduction in 1-year rehospitalizations (36.5% vs. 50.8%, p<0.001) and mortality (20.0% vs. 40.0%, p<0.001) in the CG group. CG patients also had nearly double the days alive and out of hospital (DAOH) compared to UC patients (300±100 vs. 162±145 days, p<0.001). Cox regression analysis confirmed that the CG integrated approach was a protective factor for mortality [HR 0.34, 95% CI: 0.24-0.47]. Respiratory diseases, neurological conditions, and infections were common causes of readmission.
Conclusion: Early referral to a CG outpatients service post-discharge for acute HF significantly improves outcomes, highlighting the value of integrated care for older adults with complex needs.