DECISION- Decompensated cirrhosis: identification of new combinatorial therapies based on system

Cirrhosis mortality is mainly associated with cirrhosis decompensation (development of ascites, hepatic encephalopathy, gastrointestinal haemorrhage, and progression to acute-on-chronic liver failure (ACLF). Despite multiple treatments, mortality in patients with decompensation of cirrhosis remains high. The EU-funded DECISION project aims to understand the pathophysiology of decompensation of cirrhosis leading to ACLF or death, and to decrease patient mortality. The project will study the pathophysiology of decompensation of cirrhosis by integrating results of high-throughput multi-omic profiling with comprehensive clinical data from 2 200 fully characterised patients with available standardised biological samples. DECISION will help to identify novel combinatorial therapies to prevent high mortality for patients with decompensation of cirrhosis. Finally, researchers will optimise these therapies in new animal models and then test the best combination in high-risk patients in a Phase II clinical trial.

In 2013, cirrhosis was responsible for 1.2 million deaths worldwide. This mortality is mainly due to cirrhosis decompensation, i.e. development of ascites, hepatic encephalopathy, and/or gastrointestinal hemorrhage, and its progression to acute-on-chronic liver failure (ACLF). Patients with decompensated cirrhosis receive many treatments such as intravenous and oral absorbable antibiotics, oral non-absorbable antibiotics, albumin, proton-pump inhibitors, laxatives, diuretics, betablockers, vasoconstrictors, statins, anticoagulants, steroids and antiviral agents. Despite these multiple treatments, ACLF or mortality in patients with decompensation of cirrhosis remains high (15% at day 28, 28% at day 90) because of large interindividual variability in precipitating events, in clinical presentation and in response to treatment. This heterogeneity calls for treatment personalization according to underlying mechanisms. The objective of DECISION is to enhance our understanding, at systems level, of the pathophysiology of decompensation of cirrhosis leading to ACLF or death to decrease patients' mortality at day 28.
First, DECISION will improve our knowledge of the pathophysiology of decompensation of cirrhosis by integrating results of high-throughput multi-omic profiling with comprehensive clinical data from 2,200 fully characterized patients (more than 8,600 time points) with available standardized biological samples. Second, we will identify novel combinatorial therapies for patients with decompensation of cirrhosis to prevent death. We will refine these therapies in new and/or optimized animal models and then test the best combination in high risk patients in a phase II clinical trial built in DECISION. Third, we will develop 2 tests: one predicting outcome of patients with decompensation of cirrhosis when treated with standard treatment (prognostic test); and the other identifying patients who will respond to the novel combinatorial therapy (test for response).

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