PROGETTO DI RICERCA

SAFETY AND TOLERABILITY OF YAQ-001 IN PATIENTS WITH CIRRHOSIS (CARBALIVE)

Docente proponente: Prof. Paolo Caraceni
1. BACKGROUND

The WHO estimates that over 650 million people globally and more than 29 million European citizens suffer from a chronic liver condition with in excess of 170,000 deaths from cirrhosis alone each year in Europe. Liver disease remains the 5th most common cause of death across Europe in individuals aged 45-65 years and costs more than €15.8bn per annum in total health costs and loss in economic productivity.

Alarming increases in obesity rates and an ageing population mean that liver disease will become an even greater health concern for Europe over the next decade. The three major causes of liver disease, i.e. alcoholic liver disease, NAFLD and viral hepatitis are amenable to prevention and treatment, providing an opportunity to reduce the burden of liver disease in Europe and saving lives.

Gut-derived endotoxaemia and bacterial translocation play a central role in the pathogenesis of NAFLD, the development of cirrhosis and its complications. Targeting increased bacterial translocation with poorly absorbed antibiotics is the basis for current therapeutic intervention in patients with very advanced liver disease. However, this approach has the problem of infection with resistant organisms, emergence of resistant strains of bacteria and limits its use to “treat” patients with advanced disease rather than as a preventive strategy. Minimal progress has been made with developing alternatives to this current interventional regime and a non-antibiotic strategy to prevent bacterial endotoxaemia and bacterial translocation is an unmet need.

Recent advances in synthetic activated carbon technology have resulted in the development of a carbon with a uniquely tailored porosity conferring a high absorptive capacity for gut-derived bacterial metabolites and toxins relevant to pathogenesis in liver disease (Yaq-001). The academic-industrial consortium CARBALIVE has developed a novel strategy using nanoporous carbons of tailored porosity, originally developed by MAST (US 2010/0029795) in a FP5 project-BRPR-CT97-0561, which is a safe approach that has been shown to reduce bacterial translocation. Yaq-001 is highly absorbent, synthetically derived spherical carbon with a pore size distribution relevant to the adsorption of gut-derived pathogenic factors relevant to pathogenesis of liver disease. The bimodal porosity is within meso/macroporous (> 2nm) and microporous (< 2nm) range. The larger meso/macropores allow removal of larger biological relevant molecules such as bacterial endo- and exo-toxins together with inflammatory cytokines. The micropores adsorb other pathogenic mediators such as acetaldehyde and indoles (exact composition by intellectual property protected).

The large surface area allows for favourable adsorption kinetics.

UCL has performed a range of preclinical investigations that have demonstrated the proof-of-concept and validated the therapeutic potential of the product in clinically relevant animal models of
advanced chronic liver disease and NAFLD. The results of these studies confirm that Yaq-001 has several beneficial effects on pathophysiological parameters of liver disease.

2. AIM OF THE PROJECT
The aim of this first-in-human clinical investigation is to provide data on the safety and tolerability for two doses of Yaq-001 in cirrhotic patients. It is anticipated that these data will provide sufficient information to allow for the design of subsequent performance and safety studies. The main objective of the trial is to assess the safety and tolerability of Yaq-001 throughout the three months’ treatment period, while secondary objectives are: (i) assessment of changes in blood endotoxin activity; (ii) assessment of changes in organ function; (iii) assessment of changes in nutritional status.

3. METHODS
This is an international, European multicentre double-blinded placebo-controlled dose-escalating study. To mitigate risk, the two planned dose levels will be utilized in sequential groups of patients, with oversight by DSMB. Cirrhotic patients with diuretic-responsive ascites are the target population for Yaq-001, making it desirable to understand the safety of the device in this population to more optimally determine the dose. Obtaining safety in healthy volunteers may not be relevant given that pathological bacterial translocation and intestinal dysbiosis does not occur in healthy patients with normal liver function.

The total duration of the study is estimated to be approximately 12 months from screening of first patients until study completion of the last patient.

Cirrhotic patients with diuretic-responsive ascites will be randomized to:
- Standard medical treatment + Yaq-001 or
- Standard medical treatment + placebo of Yaq-001

Two cohorts, with 28 patients per cohort, will receive either Yaq-001 or matching placebo. 56 cirrhotic patients with diuretic-responsive ascites will be enrolled (randomized to treatment). Study patients will be dosed for 12 weeks. Investigational sites specialized in the management of patients with liver cirrhosis will participate in this trial.

- Cohort 1 (1:1 randomization)
  - Standard medical treatment + Yaq-001 (4 g/ day) – n= 14.
  - Standard medical treatment + placebo-control (placebo for 4 g of Yaq-001/ day) – n= 14.
- Cohort 2 (1:1 randomization)
- Standard medical treatment + Yaq-001 (8 g/day) – n= 14.
- Standard medical treatment + placebo-control (placebo for 8 g of Yaq-001/ day) – n= 14.

4. EXPECTED RESULTS
Based on pre-clinical data, the expected clinical benefits for cirrhotic patients are: (i) an improvement in organ function: kidney, liver, brain, intestinal and immune; (ii) a reduction in blood endotoxin activity; (iii) a reduction in episodes of hepatic decompensation; (iv) an improvement in nutritional status.
ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI SCIENZE MEDICHE E CHIRURGICHE

PIANO DI FORMAZIONE CONNESSO AL PROGETTO DI RICERCA

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Il borsista svolgerà l’attività connessa al progetto presso l’U.O. Semeiotica Medica - Prof. Trevisani f.f.. In particolare, il borsista sarà inserito in uno studio multicentrico finanziato dall’Unione Europea finalizzato a valutare la sicurezza e la tollerabilità di una nuova strategia terapeutica basata sulla somministrazione di Yaq-001 nel paziente con cirrosi epatica non complicata. La fase di attivazione del centro e arruolamento dei pazienti per lo studio di safety inizierà a nei primi mesi del 2018.

Il borsista sarà impegnato nell’attività di raccolta e revisione dei dati clinici relativi ai pazienti arruolati nel protocollo.

Il processo di formazione si svilupperà su diversi aspetti di natura etica, clinica e pratica connessi allo studio. In particolare le attività specifiche saranno:

- screening dei soggetti seguiti presso l’Ambulatorio Cirrosi/OLT dell’U.O. Semeiotica Medica e verifica della sussistenza dei criteri di inclusione/esclusione secondo le modalità specificate nel protocollo;
- revisione dei dati clinici dei pazienti arruolati raccolti nell’ambito della visita di inclusione nello studio e nel corso delle visite di follow-up;
- monitoraggio del livello di aderenza alla terapia prevista e dell’andamento clinico dei pazienti, con particolare riguardo alla comparsa di eventi avversi alla terapia e complicanze della cirrosi;
- gestione e programmazione della raccolta di campioni clinici ai fini della costituzione della biobanca dei campioni raccolti nell’ambito dello studio.

In tutte le fasi del progetto, il borsista sarà affiancato da personale medico strutturato che ne supervisionerà l’operato.