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Yaq-001 positively impacts gut microbiome composition, virulence, antimicrobial resistance gene profile resulting in significant effects on ammonia, endotoxemia and inflammation in cirrhosis patients

Jinxia Liu1,2, Jose G Guevara*3,Jane Macnaughtan*1, Yi Jin3, Frederick Clasen3, Annarein JC Kerbert 1, Theo Portlock3, Javier Martinez4,5,Abeba Habtesion1,Alexandra Phillips1,Francesco De Chiara1, Ganesh Ingavle6,7,Cesar Jimenez5, Giacomo Zaccherini 8,9, Katherine Husi10, Miguel Rodriguez-Gandia4, Paul Cordero-Sanchez 7, Junpei Soeda1, Jude A Oben 1, Karen Church11, Jia V. Li 12 ,Aarti Jalan 13, Pere Gines 14, Elsa Sola14, Simon Eaton15, Carrie Morgan 16, Thomas Avery 11, Michal Kowalski 11, Daniel Green 11, Amir Gander 17, Lindsey Ann Edwards18,19, I. Jane Cox20,21, Helena Cortez-Pinto 22,Reiner Wiest10, Francois Durand 23, Paolo Caraceni8, Roberto Elosua24, Joan Vila24,Marco Pavesi 25, Vicente Arroyo 25,Nathan Davies 1, Rajeshwar P Mookerjee1, Victor Vargas 5, Susan Sandeman 6, Gautam Mehta 1, Julian R. Marchesi 26, Agustin Albillos 27, Fausto Andreola 1, Rajiv Jalan#1,25

Affiliations

1 Liver Failure Group, UCL Institute for Liver and Digestive Health, Upper third floor, Royal Free Campus, Rowland Hill Street, Hampstead, London, NW3 2PF.
2 Department of Gastroenterology, Affiliated Hospital of Nantong University, Nantong, 226001, China.
3 Centre for Host-Microbiome Interactions, Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, SE1 9RT, UK.
4 Hospital Ramón y Cajal, IRYCIS, CIBEREHD, Universidad de Alcalá, Madrid, Spain
5 Liver Unit, Hospital Vall d'Hebron, Universitat Autónoma, CIBERehd, Barcelona, Spain
6 Centre for Regenerative Medicine and Devices, School of Applied Sciences, University of Brighton, Brighton, East Sussex, BN2 4GJ, UK.
7 Symbiosis Centre for Stem Cell Research (SCSCR), Symbiosis School of Biological Sciences (SSBS), Symbiosis International (Deemed University), Pune 412115, India.
8 Department of Medical and Surgical Sciences, University of Bologna, Italy
9 Unit of Semeiotics, Liver and Alcohol.related Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy
10 Gastroenterology, University Hospital Bern, CH
11 Yaqrit Discovery Limited. The Elms Courtyard, Bromesberrow, Ledbury, United Kingdom, HR8 1RZ
12 Section of Nutrition, Division of Digestive Diseases, Department of Metabolism, Digestion and Reproduction, Hammersmith Hospital, Du Cane Road, London, W12 0NN.
13 Kings College Hospital, 125 Coldharbour Lane, London SE5 9NU, UK London
14 Liver Unit, Hospital Clinic of Barcelona, IDIBAPS, Faculty of Medicine and Health sciences, University of Barcelona. CIBEReHD
15 Institute of Child Health, University College London
16 Rarity Discovery Limited. The Elms Courtyard, Bromesberrow, Ledbury, United Kingdom, HR8 1RZ
17 Tissue Access for Patient Benefit: ROYAL FREE HOSPITAL
18 Centre for Host Microbiome Interactions, King's College London, Faculty of Dentistry, Oral & Craniofacial Sciences, Guy's Tower, Guy's Hospital, Great Maze Pond, London, SE1 1UL, UK
19 Institute of Liver Studies, School of Immunology and Microbial Sciences, Faculty of Life Sciences and Medicine, King's College London, 125 Coldharbour Lane, London SE5 9NU, UK
20 The Roger Williams Institute of Hepatology, Foundation for Liver Research, 111 Coldharbour Lane, London SE5 9NT
21 Faculty of Life Sciences and Medicine, King's College London, London, UK
22 Clínica Universitária de Gastrenterologia, Laboratório de Nutrição, Faculdade de Medicina, Universidade de Lisboa, Portugal
23 Hepatology and Liver Intensive Care, Hospital Beaujon, Clichy, University paris Cité, Paris, France
24 C/ de Joan Güell, 184, Les Corts, 08028 Barcelona, Spain
25 European Foundation for the Study of Chronic Liver Failure (EF Clif), Barcelona
26 Division of Digestive Diseases, Department of Metabolism, Digestion and Reproduction, St Mary's Hospital, Imperial College London, South Wharf Road, London, W2 1NY
27 Department of Gastroenterology and Hepatology, Hospital Universitario Ramon y Cajal, Universidad de Alcalá, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain

Contact information

Rajiv Jalan, UCL Institute for Liver and Digestive Health, Upper third floor, Royal Free Campus, Rowland Hill Street, Hampstead, London, NW3 2PF. Email: r.jalan@ucl.ac.uk.

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Introduction

Yaq-001 is a novel, non-absorbable, gut-restricted nanoporous carbon bead adsorbent. Pre-clinical studies demonstrated its ability to reduce fibrosis, portal hypertension, and organ dysfunction, partially by restoring dysbiotic gut microbiome composition and endotoxemia. A Phase 2 clinical trial confirmed its safety in patients with cirrhosis.

Aim

The aims of this study were to evaluate the effect of Yaq-001 on the gut microbiome and its association with ammonia metabolism, inflammation and endotoxemia.

Method

28-patients with compensated cirrhosis were randomized (double-blind) to receive Yaq-001 (4g once daily) or Placebo. Gut microbiome and biomarker analyses at baseline, after 4-weeks and after 12-weeks were performed. Shotgun sequence reads of the microbiome samples were mapped against the Integrated Gene Catalog of human gut microbiota to generate a gene count table and a species abundance table. Changes in biomarkers and relationship with microbiome composition were assessed.

Results

Yaq-001 was safe and no differences in liver function were observed. Alpha or beta diversity and the distribution distances of the different pairs at different time points were unaltered. Yaq-001 increased the abundance of bacteria associated with improved gut health such as *Adlercreutzia equolifaciens* (p<0.05), a bacterium with anti-inflammatory properties commonly depleted in liver disease and decreased abundance of bacteria associated with infections and poor outcomes such as *Klebsiella pneumonia* and *Streptococcus mutans* (p<0.05 each). Yaq-001 impacted positively and significantly on virulence factors such as siderophores, fimbriae structures and lipopolysaccharides (LPS) that are associated with inflammation and invasion (p<0.05 each). Systemic LPS, NGAL, LBP, creatinine and ammonia showed the highest positive correlations with the virulence factors (r>.28, p-<0.025 each). Antibiotic resistance genes (ARGs) that are linked with negative disease outcomes, decreased in the Yaq-001 group. One gene associated with secondary bile acid metabolism decreased in the Yaq-001 group and showed significant correlations with serum and fecal secondary bile acid concentrations (r >0.5, p<0.001).

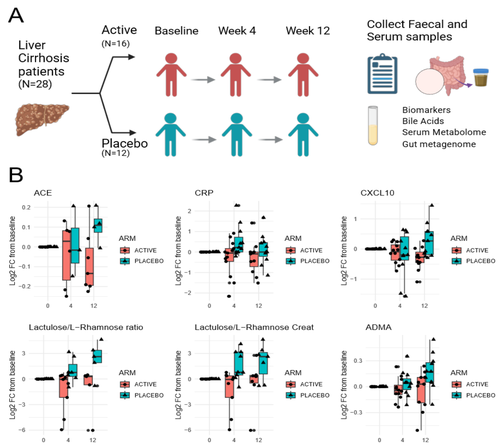

Figure 1: Experimental design and Serum Biomarkers improving after Carbalive treatment.

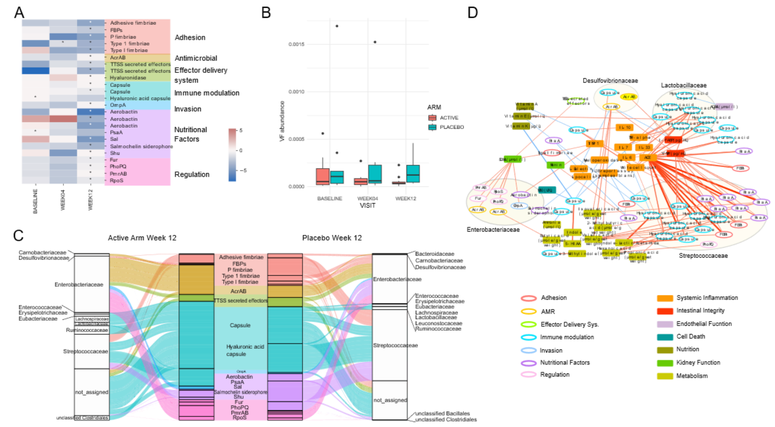

Figure 2. Virulence Factors decreasing after Carbalive treatment.

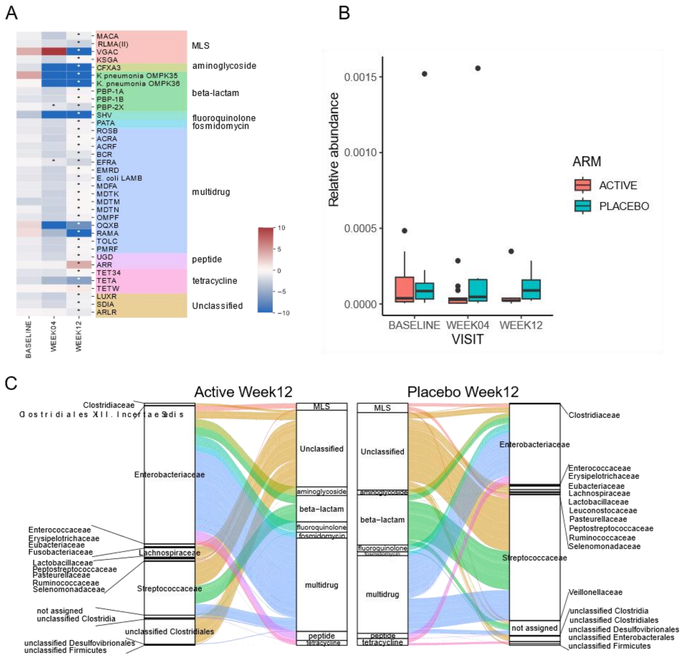

Figure 3: Antibiotic Resistance Genes decreasing after Carbalive treatment.

Conclusions

The results show that Yaq-001 impacts positively on the composition of the microbiome, significantly reduces its virulence and ARGs resulting on impacts on systemic inflammation and endotoxemia. Late phase clinical trials in cirrhosis are justified.