Targeting the gut-liver axis in liver disease

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Keywords: Gut-liver-axis; Bacterial translocation; Liver injury; Fibrosis; Cirrhosis; Bile acids; Microbiome; Incretines; Pre-, probiotics; Faecal microbial transplantation.

Received 27 March 2017; received in revised form 4 May 2017; accepted 5 May 2017

Summary

The gut-liver axis is widely implicated in the pathogenesis of liver diseases, where it is increasingly the focus of clinical research. Recent studies trialling an array of therapeutic and preventative strategies have yielded promising results. Considering these strategies, the armamentarium for targeting the gut-liver axis will continue to expand. Further clinical trials, translated from our current knowledge of the gut-liver axis, promise an exciting future in liver treatment.

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Introduction

Open to the outer environment, the gut harbours a microbiome containing several-fold more genetic material than the human genome. It produces a myriad of metabolites, as well as hormones and peptides. The liver is at the nexus between this vast source of nutrients, toxins and hormones, and the rest of the body. Unsurprisingly, in experimental models and in vitro systems, the gut-liver-axis has been demonstrated to contribute to the pathogenesis of most liver diseases, such as alcoholic and non-alcoholic fatty liver disease (NAFLD), steatohepatitis (NASH), cholestatic liver diseases, hepatocellular carcinoma (HCC), acute-on-chronic liver failure, progression to fibrosis/cirrhosis and complications of cirrhosis. Therapeutic approaches can be grouped into modulation of the microbiota, bile acid (BA) pool and/or its signalling, gut lumen adsorptive strategies, bariatric procedures, incretins and miscellaneous (e.g. prokinetics). However, investigations in humans are key. Thus, this article will highlight the most recent human studies and clinical trials targeting the gut-liver axis. A list of ongoing (not yet published) trials is presented in Table 1. Moreover, we take the liberty of encouraging clinical trials on unestablished concepts.

Background: Pathophysiology

"Whatever comes from the gut enters the liver; the portal circulation is the afferent and the biliary tree is the efferent of the gut-liver-axis" (Fig. 1): The liver is the recipient and filter of nutrients, bacterial products/toxins and metabolites from the intestine. We are becoming increasingly aware of interactions between the gut, liver, immune system and metabolism. For instance, the term "metabolic endotoxaemia" has been coined since Cani et al. discovered that the microbiome is involved in the onset of insulin resistance, low-grade inflammation and diabetes.1 This stems from the observation that constituents of gram-negative bacteria, which are present in the blood stream at very low levels because of translocation from the gut, could trigger inflammation and alter glucose metabolism.1 A complete list and overview of all the different components or metabolic products of gut bacteria, products, intestinal hormones, peptides and gut-derived neurotransmitters are beyond the scope of this article. Therefore, this article focuses on pathogen/microbe-associated molecular patterns (P/MAMPs), of which bacterial lipopolysaccharides (LPS), peptidoglycans, flagellin and bacterial DNA are prototypical.

The immune system recognises P/MAMPs via pattern recognition receptors, such as toll-like receptors and nucleotide-binding oligomerisation domain like receptors (NLR). To oversimplify, an increased inflow and/or susceptibility to P/MAMPs via pathological bacterial translocation induces a pro-inflammatory intrahepatic milieu driven by
### Table 1. Ongoing clinical trials targeting the gut-liver-axis.

| Medication | Mechanism | Trial phase | Target population | Primary Endpoint | Acronym/ reference |
|------------|-----------|-------------|--------------------|------------------|-------------------|
| Amoxicillin + clavulanic acid | Antibiotic | Phase III | Alcoholic Hepatitis MD > 32 | Survival at 2 mo | AntibioCor<sup>30</sup> |
| Ciprofloxacin | Antibiotic | Phase IV | Severe alcoholic hepatitis | Death at 28 days, 3 and 6 mo | 32 |
| Rifaximin SSD | Antibiotic | Phase II | Early decompensated cirrhosis | Mortality or liver-related hospitalisation | 50 |
| Rifaximin | Antibiotic | Phase III | Alcoholic Hepatitis MD > 32 | Bacterial infections after 90 d | RIFA-AAH<sup>1</sup> |
| Rifaximin | Antibiotic | Phase IV | Liver cirrhosis | Death, LTx, number complications | 54 |
| Rifaximin | Antibiotic | Phase IV | Decompensated cirrhosis, HVPG > 10 mmHg | Change HVPG | 55 |
| Rifaximin | Antibiotic | Phase III | Cirrhosis with TIPS | First episode of covert encephalopathy in patients treated by TIPS | PRPET<sup>36</sup> |
| Rifaximin | Antibiotic | Phase III | Cirrhosis with low-protein ascites plus risk factor | 12 mo mortality | ProPLARifax<sup>37</sup> |
| Rifaximin | Antibiotic | Phase III | Cirrhosis with gastroesophageal bleeding | Composite (complication cirrhosis or death) in 8 wk | RFXM<sup>38</sup> |
| Rifaximin | Antibiotic | Phase IV | Cirrhosis with remission from overt HE | Time to first Hepar Encephalopathy (HE) breakthrough episode | 59 |
| Rifaximin | Antibiotic | Phase IV | Liver resection (≥ 4 segments) | Liver function | Arrow<sup>31</sup> |
| Rifaximin | Antibiotic | Phase IV | NAFLD/NASH ± fibrosis stage 0–3 | Serum endotoxin | 60 |
| Flagyl or vancomycin | Antibiotic | Phase IV | Cirrhosis with HE | Neutrophil spontaneous oxidative burst ex vivo | RIFSYS<sup>33</sup> |
| Vancomycin | Antibiotic | Phase IV | Children with PSC/Overlap-syndrome | Liver function test | 40 |
| Solithromycin | Antibiotic | Phase II | Recurrent PSC post-LTx | Liver function test at 12 wk | 39 |
| Not stated | FMT | Phase II | PSC | Liver biochemistry (AP, AST, ALT), bilirubin | 104 |
| Rectal enema | FMT | Phase I | Cirrhosis with recurrent HE | Safety, tolerability | 95 |
| Endoscopic duodenal application | FMT | Phase I | NASH | Hepatic steatosis | 103 |
| Nasojejunal tube | FMT | Not provided | NASH-related decompensated cirrhosis | Complications of cirrhosis | 101 |
| Endoscopic duodenal application | FMT | Phase II | NAFLD | HOMA score | 102 |
| Rectal enema | FMT | Phase I | Cirrhosis | Feasability | PROFIT<sup>100</sup> |
| Jejunal tube application daily for 7 d | FMT | Phase II | Liver Transplant Recipient (>30 d post-LTx) | Feasability | 99 |
| Oligofructose-enriched Inulin | Pre-biotic | - | NAFLD | Survival at 3 mo | 96 |
| Oligofructose-enriched Inulin | Pre-biotic | - | Liver injury, fat, fibrosis | 65 |
| VSL3 | Pro-biotic | - | NAFLD | Liver fat, injury, inflammation | 66 |
| Bio-25/ Subherb | Pre-biotic | - | NAFLD and sleeve gastrectomy | Ultrasound liver fat | 71 |
| Lactobacillus rhamnosus and Bifidobacterium animalis | Pro-biotic | - | Post-LTx-metabolic syndrome | Change total body weight | 72 |
| Lactobacillus acidophilus ATCC SD5221 and 1.109 Bifidobacterium lactis HN019 | Pro-biotic | - | NAFLD | Liver biopsy 6 mo | 76 |
| Lactobacillus spp | Pro-biotic | - | NAFLD | Plasma LPS 12 wk | 77 |

(continued on next page)
