Clinical Trial Watch

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Targeting the gut-liver axis in liver disease

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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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Key point

The gut-liver-axis has matured from a pathophysiological concept, with experimental data on mechanisms and intrahepatic effects, to clinical trials on therapeutic and preventive measures aiming to improve prognosis of multiple chronic liver diseases.

"Always trust your gut – it knows what your head and liver has not yet figured out"

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, the 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 endotoxemia" 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 focusses 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[36]
Ciprofloxacin	Antibiotic	Phase IV	Severe alcoholic hepatitis	Death at 28 days, 3 and 6 mo	[37]
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[51]
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[56]
Rifaximin	Antibiotic	Phase III	Cirrhosis with low-protein ascites plus risk factor	12 mo mortality	ProPILARifax[57]
Rifaximin	Antibiotic	Phase III	Cirrhosis with gastroesophageal bleeding	Composite (complication cirrhosis or death) in 8 wk	RFXM[58]
Rifaximin	Antibiotic	Phase IV	Cirrhosis with remission from overt HE	Time to first Hepatic Encephalopathy (HE) breakthrough episode	[59]
Rifaximin	Antibiotic	Phase IV	Liver resection (⩾4 segments)	Liver function	Arrow[61]
Rifaximin	Antibiotic	Phase IV	NAFLD/NASH ± fibrosis stage 0–3	Serum endotoxin	[60]
Rifaximin	Antibiotic	Phase IV	Cirrhosis with HE	Neutrophil spontaneous oxidative burst *ex vivo*	RIFSYS[53]
Flagyl or vancomycin	Antibiotic	Phase IV	Children with PSC/ Overlap-syndrome	Liver function test	[40]
Vancomycin	Antibiotic	Phase IV	Recurrent PSC post-LTx	Liver function test at 12 wk	[39]
Solithromycin	Antibiotic	Phase II	NASH	Safety, NAFLD activity score in histology	[222]
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]
Nasojejunal tube	FMT	Phase II	NAFLD	HOMA score	[102]
Endoscopic duodenal application	FMT	Phase III	Cirrhosis	Feasability	PROFIT[100]
Rectal enema	FMT	Phase I	Liver Transplant Recipient (>30 d post-LTx)	Feasability	[99]
Jejunal tube application daily for 7 d	FMT	Phase II	Severe alcoholic hepatitis, steroid non-responder/ intolerant MD >32	Survival at 3 mo	[96]
Oligofructose-enrichred Inulin	Pre-biotic	-	NAFLD	Liver injury, fat, fibrosis	[65]
Oligofructose-enrichred Inulin	Pre-biotic	-	NAFLD	Liver fat, injury, inflammation	[66]
VSL3	Pro-biotic	-	NAFLD	NAFLD activity score at 1 yr	[70]
Bio-25/Subherb	Pro-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]

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