Targeting the gut-liver axis in liver disease

Reiner Wiest1,*, Agustin Albillos2, Michael Trauner3, Jasmohan S. Bajaj4, Rajiv Jalan5

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, 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.

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

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. 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. 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.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Trial phase</th>
<th>Target population</th>
<th>Primary Endpoint</th>
<th>Acronym/reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin + clavulanic acid</td>
<td>Antibiotic</td>
<td>Phase III</td>
<td>Alcoholic Hepatitis MD ≥ 32</td>
<td>Survival at 2 mo</td>
<td>AntibioCor30</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Antibiotic</td>
<td>Phase IV</td>
<td>Severe alcoholic hepatitis</td>
<td>Death at 28 days, 3 and 6 mo</td>
<td>32</td>
</tr>
<tr>
<td>Rifaximin SSD</td>
<td>Antibiotic</td>
<td>Phase III</td>
<td>Early decompensated cirrhosis</td>
<td>Mortality or liver-related hospitalisation</td>
<td>50</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Antibiotic</td>
<td>Phase III</td>
<td>Alcoholic Hepatitis MD ≥ 32</td>
<td>Bacterial infections after 90 d</td>
<td>RIFA-AAH11</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Antibiotic</td>
<td>Phase IV</td>
<td>Liver cirrhosis</td>
<td>Death, LTx, number complications</td>
<td>54</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Antibiotic</td>
<td>Phase IV</td>
<td>Decompensated cirrhosis, HVPG &gt;10 mmHg</td>
<td>Change HVPG</td>
<td>55</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Antibiotic</td>
<td>Phase III</td>
<td>Cirrhosis with TIPS</td>
<td>First episode of covert encephalopathy in patients treated by TIPS</td>
<td>PRPET66</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Antibiotic</td>
<td>Phase III</td>
<td>Cirrhosis with low-protein ascites plus risk factor</td>
<td>12 mo mortality</td>
<td>ProPILARi57</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Antibiotic</td>
<td>Phase III</td>
<td>Cirrhosis with gastrosophageal bleeding</td>
<td>Composite (complication cirrhosis or death) in 8 wk</td>
<td>RFXM8</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Antibiotic</td>
<td>Phase IV</td>
<td>Cirrhosis with remission from overt HE</td>
<td>Time to first Hepatic Encephalopathy (HE) breakthrough episode</td>
<td>59</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Antibiotic</td>
<td>Phase IV</td>
<td>Liver resection (&gt;4 segments)</td>
<td>Liver function</td>
<td>Arrow81</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Antibiotic</td>
<td>Phase IV</td>
<td>NAFLD/NASH ± fibrosis stage 0–3</td>
<td>Serum endotoxin</td>
<td>60</td>
</tr>
<tr>
<td>Flagyl or vancomycin</td>
<td>Antibiotic</td>
<td>Phase IV</td>
<td>Children with PSC/Overlap-syndrome</td>
<td>Liver function test</td>
<td>40</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Antibiotic</td>
<td>Phase IV</td>
<td>Recurrent PSC post-LTx</td>
<td>Liver function test at 12 wk</td>
<td>39</td>
</tr>
<tr>
<td>Solithromycin</td>
<td>Antibiotic</td>
<td>Phase II</td>
<td>NASH</td>
<td>Safety, NAFLD activity score in histology</td>
<td>222</td>
</tr>
<tr>
<td>Not stated</td>
<td>FMT</td>
<td>Phase II</td>
<td>PSC</td>
<td>Liver biochemistry (AP, AST, ALT), bilirubin</td>
<td>104</td>
</tr>
<tr>
<td>Rectal enema</td>
<td>FMT</td>
<td>Phase I</td>
<td>Cirrhosis with recurrent HE NASH</td>
<td>Safety, tolerability</td>
<td>95</td>
</tr>
<tr>
<td>Endoscopic duodenal application</td>
<td>FMT</td>
<td>Phase I</td>
<td>NASH</td>
<td>Hepatic steatosis</td>
<td>103</td>
</tr>
<tr>
<td>Nasojugal tube</td>
<td>FMT</td>
<td>Not provided</td>
<td>NASH-related decompensated cirrhosis</td>
<td>Complications of cirrhosis</td>
<td>101</td>
</tr>
<tr>
<td>Nasojugal tube</td>
<td>FMT</td>
<td>Phase II</td>
<td>NAFLD</td>
<td>HOMA score</td>
<td>102</td>
</tr>
<tr>
<td>Endoscopic duodenal application</td>
<td>FMT</td>
<td>Phase III</td>
<td>Cirrhosis</td>
<td>Feasability</td>
<td>PROFIT100</td>
</tr>
<tr>
<td>Rectal enema</td>
<td>FMT</td>
<td>Phase I</td>
<td>Liver Transplant Recipient (&gt;30 d post-LTx)</td>
<td>Feasability</td>
<td>99</td>
</tr>
<tr>
<td>Jejunal tube application daily for 7 d</td>
<td>FMT</td>
<td>Phase II</td>
<td>Severe alcoholic hepatitis, steroid non-responder/intolerant MD &gt;32</td>
<td>Survival at 3 mo</td>
<td>96</td>
</tr>
<tr>
<td>Oligofructose-enriched Inulin</td>
<td>Pre-biotic</td>
<td>-</td>
<td>NAFLD</td>
<td>Liver injury, fat, fibrosis</td>
<td>65</td>
</tr>
<tr>
<td>Oligofructose-enriched Inulin</td>
<td>Pre-biotic</td>
<td>-</td>
<td>NAFLD</td>
<td>Liver fat, injury, inflammation</td>
<td>66</td>
</tr>
<tr>
<td>VSL3</td>
<td>Pro-biotic</td>
<td>-</td>
<td>NAFLD</td>
<td>NAFLD activity score at 1 yr</td>
<td>70</td>
</tr>
<tr>
<td>Bio-25/Subhberb</td>
<td>Pro-biotic</td>
<td>-</td>
<td>NAFLD and sleeve gastrectomy</td>
<td>Ultrasound liver fat</td>
<td>71</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus and Bifidobacterium animalis</td>
<td>Pro-biotic</td>
<td>-</td>
<td>Post-LTx-metabolic syndrome</td>
<td>Change total body weight</td>
<td>72</td>
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<tr>
<td>Lactobacillus acidophilus ATCC SD5221 and 1.109 Bifidobacterium lactis HNO19</td>
<td>Pro-biotic</td>
<td>-</td>
<td>NAFLD</td>
<td>Liver biopsy 6 mo</td>
<td>76</td>
</tr>
<tr>
<td>Lactobacillus spp</td>
<td>Pro-biotic</td>
<td>-</td>
<td>NAFLD</td>
<td>Plasma LPS 12 wk</td>
<td>77</td>
</tr>
</tbody>
</table>

(continued on next page)