Title: Proton pump inhibitors in chronic liver disease: accomplice or bystander?

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Invited editorial:

Since the introduction of omeprazole in 1989, proton pump inhibitors (PPIs) have revolutionized the medical therapy for patients with upper gastrointestinal disorders. Initially developed as a treatment for reflux esophagitis, these inhibitors of gastric acid secretion have subsequently been used in a wide array of both acid-related and non-acid related disorders. For instance, short-term PPI therapy is indicated in eradication of *Helicobacter pylori* infection, treatment of peptic ulcer disease, stress ulcer prophylaxis in high risk patients, and following endoscopic treatment of a high-risk peptic ulcer bleeding and gastroesophageal varices. Long-term PPI therapy is indicated in treatment of severe erosive esophagitis, Barrett's esophagus, Zollinger-Ellison syndrome, PPI-responsive gastro-esophageal reflux disease, and prevention of gastrointestinal bleeding in high-risk individuals taking ulcerogenic medications. With the initial seemingly excellent safety profile, the use of PPIs have been further broadened, inevitably leading to inappropriate PPI use.

Specific to chronic liver disease, it is reported that 37-86% patients with cirrhosis were on PPIs, and as much as 34-74% of them were on PPIs without appropriate indications [1]. Patients with chronic liver disease may be on long-term PPIs for 'prevention of bleeding from portal hypertensive gastropathy' which has been shown to be ineffective [2], or simply because PPIs were inadvertently continued following an episode of upper gastrointestinal bleeding or variceal banding. Coupled with the exponential increase in PPI use worldwide, the literature regarding PPI safety has expanded enormously. Apart from causing acute interstitial nephritis, fundic gland polyps and vitamin B12 deficiency, several other adverse effects that are attributed to long-term PPIs are so far weak associations only. These include small intestine bacterial overgrowth (SIBO), spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy (HE) in cirrhotic patients, and *Clostridium difficile* infection, hypomagnesemia, bone fracture, chronic kidney disease, dementia, community-acquired pneumonia, and gastric cancer [3].

In this issue, Wang et al performed a systematic review and meta-analysis on 5 adverse clinical outcomes of PPIs in patients with chronic liver disease, including SBP, HE, infection, mortality and hepatocellular carcinoma (HCC). The authors showed that all 5 adverse events, except HCC (no conclusions could be drawn due to small number of studies), were associated with long-term PPI use. This is the first study to report a constellation of adverse clinical outcomes associated with PPIs in this patient group, with the inclusion of 47 up-to-date studies. A few prospective studies were also included, consisting of patients with compensated and decompensated cirrhosis. The findings from the included studies were consistent across different regions of the world: Asia, Europe and North America. However, the strength of association is weak judging from the adjusted odds ratios of approximately two. Most importantly, the association of long-term PPI use with the adverse clinical outcomes did not necessarily equate causality, as there were too many confounding factors that could not be adjusted with observational data.

One of these confounding factors is renal function. In all 47 studies, only 1 study adjusted for serum creatinine. However, renal function is an important predictor of mortality and HE in patients with chronic liver disease, and is a major component of the Model for End-stage Liver Disease (MELD) score. Moreover, PPIs have been reported to cause acute kidney injury and chronic kidney disease. The

possible effects of PPIs on mortality in chronic liver disease are multi-faceted. Another confounding factor is medication use. Lactulose and prophylactic antibiotics are used routinely to prevent recurrent HE and SBP, respectively. In addition, beta-blockers have been shown to be protective in cirrhotic patients, but in patients with more advanced liver disease (i.e. Child Pugh class C, decompensated cirrhosis), it may be associated with adverse outcomes. However, only few out of the 47 studies adjusted for use of medications. Finally, and perhaps the most important confounding factor, is the severity of liver disease. A proportion of patients on PPIs may have genuine indications, such as post-banding for acute variceal hemorrhage. Therefore, patients that are exposed to PPIs may actually represent those with intrinsically more advanced liver disease, and the use of PPI may in fact be a surrogate marker of portal hypertension. As portal pressure is not routinely measured, the MELD was chosen to reflect the degree of liver decompensation. However, only about half of the included studies adjusted for MELD. Without matching of baseline variables in these observational studies, PPI users had higher Child Pugh class scores, higher percentage of ascites, HE and esophageal varices, compared to non-PPI users [4]. This non-adjustable bias in severity of liver disease between PPI users and non-PPI users can only be avoided with carefully designed prospective studies with appropriate matching. Such study design could also eliminate potential immortal-time bias, since PPI use was not treated as a time-varying covariate in most published studies [5].

To prove causality of PPI in adverse clinical outcomes in patients with chronic liver disease, certain principles should be fulfilled. Biological gradient is never demonstrated, as none of the studies evaluated dose-response relationship. More clinical evidence to confirm biological plausibility is required, although PPIs have been attributed to SIBO with so far conflicting results [6,7]. Recent evidence suggested that PPI users with compensated chronic liver disease had alterations in gut microbiota similar to those with established cirrhosis (e.g. enrichment of *Lactobacillus*, *Streptococcus*, *Veillonella*, and reduction in *Ruminococcus*) [4]. Such pattern of dysbiosis, in the same manner as progression of liver disease, is hypothesized to predispose to higher risk of SBP from bacterial translocation and dysbiosis, leading to release of excessive endotoxin and microbiome-derived metabolites, i.e. pathogen-associated molecular patterns, into the portal circulation, which subsequently activate the toll-like receptor on Kupffer cells and hepatic stellate cells, in turn leading to hepatic injury and fibrogenesis. This is further echoed by a recent study that reported increased in small intestinal

Enterococcus following ethanol administration to mice that were pre-treated with oral PPI, which subsequently led to impaired control of mucosa-associated microbiota and increased bacterial translocation, eventually facilitated progression of alcoholic liver disease [8]. Moreover, PPIs were shown to weaken neutrophil and monocyte by decreasing oxidative burst, which might have contributed to attenuated systemic immunity [9]. These proposed mechanisms linking PPI use to adverse effects in patients with chronic liver disease are shown in Figure 1.

The current study by Wang et al sets the stage for further research to identify each piece of the pathophysiology puzzle. In the post-hoc analysis of a recently published randomized double blinded controlled trial of 17598 PPI vs. non-PPI user (median follow-up of 3.01 years) that looked at the cardiovascular events as the primary outcome, it showed that all the alleged PPI-related adverse effects, except enteric infections, were not significantly different between PPI users and non-PPI users [10]. These findings should take into consideration that the follow-up time was relatively short, and a significant proportion of the cohort were aspirin users that might have hampered certain adverse outcomes e.g. cancer, since aspirin is a chemo-preventive agent. To prove the alleged risks of PPI in causing SBP, HE, infection and mortality in patients with chronic liver disease, only well-designed, prospective, randomized, double-blinded trials can answer the question. Last but not least, it must be emphasized that most PPIs do not need to be taken long-term in the setting of chronic liver disease. Virtually no studies have evaluated the reversibility of PPI-related adverse clinical outcomes, i.e. reduction in risks after discontinuation of PPI in consecutive patients, owing to the clinicians' inertia to stop PPIs in a group of vulnerable patients. After all, the indication and intended duration of PPIs should be reviewed in each case. Before further evidence is available to prove the role of PPIs as the main culprit or otherwise, cautious weighing of benefits and potential risks of PPIs should be done at all times.

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Figure 1. Proposed mechanisms of adverse effects of PPI in patients with chronic liver disease