PPI therapy in liver disease progression: More cause for concern?

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The long term consequences of proton pump inhibitor (PPI) therapy have been the subject of much concern. Previous studies have described an increased risk of pneumonia (1), *Clostridium difficile* colitis (1), spontaneous bacterial peritonitis (2) and hepatic encephalopathy (2) with PPI therapy but the literature base is heterogenous and dominated by retrospective analyses.

Li *et al.* explore the association between cumulative PPI dose and disease progression both with regards to development of cirrhosis and hepatocellular carcinoma (HCC) in a large-scale retrospective analysis of patients with pre-cirrhotic hepatitis C (HCV) (3). They observed that PPI use was independently associated with a higher risk of hepatic decompensation in a dose-dependent manner; an observation not made with histamine 2 (H2) antagonist therapy. The implication is that PPI therapy most likely modulates the natural history of HCV via modulation of the gut microbiome, heightened bacterial translocation rates with excessive stimulation of profibrogenic and carcinogenic Toll-like Receptor 4 (TLR4) pathways. Whilst this mechanism is unproven in this study, the evidence for TLR4 signalling in fibrogenesis and carcinogenesis in pre-clinical models is substantial (4). Furthermore, TLR4 expression by hepatic progenitor cells and biliary epithelial cells correlate positively with fibrosis and inflammation in HCV (5).The authors also observed that PPI use was associated with a significantly increased risk of HCC. Previous studies have demonstrated increased TLR4 expression in HCC (6). Lipopolysaccharide has been shown to promote angiogenesis in a murine model of HCC via TLR4 pathways (7) and TLR4 deficiency or germ free conditions are protective against carcinogenesis (8).

That the effects of PPI therapy were independent of sustained viral response (SVR) is an important observation suggestive that PPI treatment independently influences the natural history of HCV in a manner synergistic with failure of SVR. PPIs also have the potential for drug-drug interactions with agents such as ledipasvir given insolubility at pH>4. Indeed Tapper *et al.* observed that twice daily PPI dosing was associated with a reduction in SVR12 rates (9).

The results of this study are interesting for several reasons. Firstly, and most importantly they highlight the significant risk of long term PPI therapy in this patient group. Secondly, they suggest that the microbiome plays a key role in modulating the natural history of HCV independently from SVR, implying that gut-specific targets could further prevent decompensation and HCC. The differential effect of PPIs vs H2 antagonist treatment is more likely to be a function of degree of acid suppression rather than non-gastric proton pump inhibition. Whilst PPIs have pleiotropic effects, they are in general anti-inflammatory and anti-oncogenic and therefore do not mechanistically explain the accelerated disease progression observed in this study.

Whilst the study is important and adds to the weight of evidence pointing to the deleterious effects of PPIs, the study is retrospective in nature and requires prospective validation. Nonetheless, the premise that PPIs promote bacterial translocation and accelerate disease progression is relevant and supports the conclusion that PPIs should be stopped or replaced by H2 antagonists where possible.

References

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