LETTERS TO THE EDITORS

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REFERENCES

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Letter: *Helicobacter pylori* in proton pump inhibitor-associated biliary disease

EDITORS,

Min et al. in their cohort study, proposed the role of proton pump inhibitors (PPI) as a risk factor of cholangitis, especially during the period of their use. This observational result could include unrecognized confounders, one of which to consider being the overlap between *Helicobacter pylori* infection (*Hp-I*) and the conditions treated using a PPI: dyspepsia, peptic ulcer disease and, at least in some populations, gastro-oesophageal reflux disease—Barrett’s oesophagus—oesophageal cancer sequence are associated with *Hp-I* and represent the most frequent indications for PPI prescription. Moreover *Hp-I* is involved in PPI-related disorders discussed by the authors.1-3

The impact of *Hp-I* with biliary tree diseases has been described. Bile stasis has primarily been connected with hepatobiliary *Hp* contamination, thus leading to a threefold risk of chronic lithiasis and cholecystitis, triggered by a perpetual inflammation of the gallbladder. In this respect, our data indicated *Hp* presence in gallbladder tissue in 19.33% of patients who were submitted to cholecystectomy due to lithiasis,6 while chronic biliary *Hp-I* has been identified in 75% of patients with gallbladder cancer.7

The proposed routes of contamination, although unproved, include ascending migration through the sphincter of Oddi and haematogenous spread to the liver and then excretion into bile. In this respect, the potential influx of activated monocytes infected with *Hp* (due to defective autophagy) from the circulation into the gallbladder might relate to gallbladder-related pathologies (“Trojan horse” pathway); biliary excretion of *Hp* invaded macrophages might trigger proinflammatory cytokine release, oxidative stress and inflammation, thus promoting gallstone formation and its complications (cholecytis/cholangitis/pancreatitis). Additionally, biliary *Hp-I* could provoke an imbalance of apoptotic cellular processes and contribute to biliary carcinogenesis. In vitro data support this, indicating that *Hp* promotes cell proliferation and suppresses apoptosis of human intrahepatic biliary epithelial cells by increasing reactive oxygen species release.8 Finally, the authors suggested as a possible pathogenetic mechanism of PPI-related cholangitis, the imbalance between the normal small intestine microbiota and the bacterial overgrowth due to gastric acid suppression.1 Nevertheless, *Hp-I* seems to cause more significant alterations in gut microbiota than PPI use, thus contributing to biofilm formation.9

*Hp-I* has also been associated with a plethora of extragastric conditions, such as cardiovascular and neurodegenerative diseases, glaucoma, gastrointestinal tract oncogenesis, non-alcoholic fatty liver disease and hepatic encephalopathy.10 Therefore, it seems reasonable to consider adjusting for the presence of *Hp-I* as a potential cofounder in PPI-related disorders, as it is perhaps potentially relevant to a wide range of conditions necessitating their use.

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LINKED CONTENT

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Letter: is tenofovir superior to entecavir for hepatocellular carcinoma prevention in chronic hepatitis B?

EDITORS,

There has been a handful of studies that have demonstrated that entecavir and tenofovir disoproxil fumarate (TDF) monotherapy are effective treatments for chronic hepatitis B (CHB) to reduce the risk of liver cirrhosis, hepatocellular carcinoma (HCC) and all-cause mortality. Therefore, these two anti-viral drugs are both recommended by international guidelines and have been widely used in clinical practice. In recent issues of Alimentary Pharmacology & Therapeutics, two studies showed that TDF reduces the incidence of HCC in CHB patients.1,2 However, neither of these two studies directly compared the efficacy of TDF with entecavir. The efficacy of TDF and entecavir in preventing HCC in CHB patients is controversial in recent large cohort studies.

We systematically searched PubMed for studies that directly compared TDF with entecavir on the risk of HCC. Because these two drugs were not approved for clinical use at the same period of time, follow-up duration and baseline variables may be not comparable between the two groups. Therefore, only studies using propensity score analysis may be included in the analysis. Risk ratios (RRs) and 95% confidence intervals (95% CIs) were calculated to compare the incidence of HCC between CHB patients who underwent TDF and entecavir monotherapy.

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