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Journal Club

Acid-suppressive Medications and Risk of Esophageal Adenocarcinoma in Patients With Barrett's Esophagus

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Summary

Barrett's esophagus (BE), characterized by a metaplastic change in the esophageal mucosa from a squamous to columnar mucosa with intestinal metaplasia, is the dominant pre-malignant lesion associated with esophageal adenocarcinoma (EAC), and BE confers a 30-125 folds higher risk of EAC. Although acid-suppressive medications can be used as a chemopreventive strategy for patients with BE, their effect on the incidence of EAC has been controversial.[1]

Recently, Singh et al[2] reported a systematic review and meta-analysis of all studies that had investigated the association between acid-suppressive medications and EAC/high-grade dysplasia (HGD) in patients with BE. In a meta-analysis of 7 studies (2813 patients with BE, 317 cases of EAC/HGD), proton pump inhibitors (PPIs) were associated with a 71% risk reduction in progression to EAC/HGD among patients with BE (adjusted odds ratio, 0.29; 95% confidence interval, 0.12-0.79). This PPI effect was duration-dependent; PPI use extending beyond 2-3 years after BE diagnosis was associated with a lower risk of EAC/HGD, whereas PPI use for a shorter period was not associated with a protective effect. In addition, the PPI effect was independent of the presence of erosive esophagitis or reflux symptoms or the concomitant use of other putative chemopreventive agents such as aspirin and statins. However, histamine receptor antagonists had no significant effect on EAC risk modification in patients with BE. Therefore, the authors suggested that PPI use should be considered as a chemopreventive method in patients with BE.

Comments

Although BE is an important precursor of EAC, only a small fraction of patients with BE will develop EAC. Routine endoscopic surveillance of patients with BE and endoscopic therapy for the subset of patients with early EAC and HGD are recommended.[1] However, this endoscopic approach is expensive and limited by suboptimal adherence and access. Therefore, relatively inexpensive and effective chemopreventive strategies have

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recently been suggested; however, the role of chemoprevention in BE remains controversial.[3]

In addition to acid-suppressive medications, NSAIDs, aspirin, metformin, and statins have been studied as potential chemopreventive agents in BE.[4] Although there is some convincing evidence for a potential role of NSAIDs in EAC prevention, the overall benefit-to-harm ratio remains unfavorable.[4] Metformin has effects on esophageal cancer cells in vivo, but clinical data in the context of EAC has shown a negative effect.[5] Although aspirin and statins have been reported to be associated with a lower risk of EAC/HGD in patients with BE, the effect size is moderate, with an estimated risk reduction of 32-41%.[6,7]

In the present study, the authors showed a more definite reductive effect of PPI use on progression to EAC/HGD, specifically a duration-dependent 71% risk reduction. As such, how do PPIs exert anti-neoplastic effects in BE? The suggested primary chemopreventive mechanism of PPIs is reduction in intra-esophageal acid and bile exposure and consequent promotion of esophageal mucosal healing. PPIs also exhibit anti-inflammatory properties independent of their acid-suppressive effects, which might also contribute to the chemopreventive effect of these agents against EAC.[8] Furthermore, long-term PPI treatment can induce the formation of esophageal squamous islands in patients with BE[9] and may decrease the length of the BE segment.

In contrast, it is theoretically possible that prolonged PPI treatment can induce hypergastrinemia, possibly leading to induce proliferation and cyclooxygenase-2 up-regulation, potentiating esophageal carcinogenesis.[10] Although gastrin might enhance epithelial restitution in Barrett's mucosa, it does not promote the proliferation and expansion of Barrett's segments during long-term PPI treatment.[11] Therefore, until now, clinical studies have provided no evidence that prolonged PPI treatment promotes esophageal carcinogenesis.

Based on their chemopreventive effects, PPIs should be considered for primary chemoprevention in patients with BE and multiple risk factors for progression to EAC such as long-segment BE, low-grade dysplasia, central adiposity, smoking, or advanced age. Although the exact dose and therapeutic efficacy endpoint remain unknown, a regular once-daily PPI therapy dose might be appropriate. Of course, a cost-effectiveness analysis of the chemopreventive effects of PPI in patients with BE should be performed in the near future. However, currently and given concerns about adverse effects, including the potential long-term risks associated with prolonged PPI use, the risks and benefits of PPI use as a chemopreventive strategy would need to be carefully discussed with patients with BE.

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