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Barrett’s oesophagus, proton pump inhibitors and gastrin: the fog is clearing

Ernst J Kuipers1,2

The incidence of Barrett’s oesophagus is rising rapidly.1 The presence of metaplastic tissue in the lower oesophagus is by itself an asymptomatic condition, but predisposes to oesophageal adenocarcinoma. Long-term cohort studies reported that the incidence of oesophageal cancer among patients with Barrett’s oesophagus approximates 4 per 1000 patient years follow-up, and that ultimately 5–7% of patients with Barrett’s oesophagus die of this condition.2 The majority of patients with Barrett’s oesophagus suffer from chronic gastro-oesophageal reflex, and therefore often receive proton pump inhibitor (PPI) treatment. The effect of such treatment on Barrett’s mucosa and the risk for progression to cancer have been much studied and debated. Reduction of oesophageal acid exposure decreases inflammation and proliferation, increases cell differentiation within the Barrett’s segment, and might in theory reverse metaplasia, in particular in areas of ulceration. On the other hand, PPI therapy interferes with oesophageal exposure to secondary bile acids, and increases gastrin, which may induce proliferation, COX-2 upregulation, and perhaps expansion of metaplasia.3 Along this line it has been suggested that PPIs may promote progression of Barrett’s metaplasia and progression to cancer. We thus have a body of seemingly conflicting research data, which are difficult to align and provide clinicians with a foggy image of this clinically relevant topic. Several hurdles obstruct progression of our knowledge. These include the lack of a suitable animal model, the difficulty to perform randomised controlled trials when most patients require acid suppression for symptom control, and the need for large, long-term studies when looking at relevant end points of dysplasia and cancer.

In this issue of Gut, Obszynska and colleagues (see page 156) were nevertheless able to considerably increase our knowledge on this important topic.4 They performed in vitro and in vivo studies, both cross-sectional and long-term, focusing on the role of gastrin and its CCK2 receptor (CCK2R) in Barrett’s oesophagus. These were based on the hypothesis that gastrin and CCK2R may play a key role in the expansion of Barrett’s oesophagus and the progression to cancer. The authors therefore examined the in vivo expression of gastrin and CCK2R receptor in Barrett’s metaplasia and adjacent mucosa, the in vitro effects of exogenous gastrin and CCK2R on several relevant cellular processes, and finally the relation between long-term PPI therapy, expression of gastrin and CCK2R, and changes in length of the Barrett’s segment. They found that gastrin and CCK2 were progressively expressed in squamous oesophagus, Barrett’s metaplasia, and stomach. In vitro experiments with an oesophageal adenocarcinoma cell line next showed that physiological levels of gastrin did not increase proliferation. However, elegant experiments in a tissue growth assay showed that the same levels of gastrin did induce cellular migration. This phenomenon was not affected by blocking of proliferation, but was impaired by a CCK2 receptor antagonist, antagonising the gastrin stimulus. Similar experiments had no effects on a oesophageal squamous cancer cell line. Finally, studies in patients with Barrett’s oesophagus showed no changes in tissue and circulating gastrin levels, nor in mucosal CCK2 receptor levels during 2 year low- or high-dose omeprazole treatment. This treatment also did not induce any changes in length of the Barrett’s segments. Based on these results, the authors conclude that gastrin has no clear effects on the oesophageal squamous mucosa, but enhances epithelial restitution in Barrett’s mucosa. However, the lack of effect on proliferation and the lack of expansion of Barrett’s segments during long-term PPI treatment supports the clinical safety of such treatment for this condition.

These data fit in with previous studies. For instance, various studies looked at changes in length of Barrett’s segment during prolonged PPI therapy. Most of these were uncontrolled and small, yet one study had a randomised, double-blind design comparing 2 year treatment with 40 mg omeprazole twice daily versus 150 mg ranitidine twice daily.5 High-dose omeprazole treatment was associated with the appearance of squamous islands in the Barrett’s segment of many patients, and with a tendency for reduction in Barrett’s length. The squamous islands were also observed in most uncontrolled studies. The reduction in length was supported by a recent retrospective survey from the US, reporting that prior PPI use predicted a shorter length of newly diagnosed Barrett’s segments.6

The paper in this journal4 elegantly builds on this previous literature, together showing that PPI therapy has several effects on Barrett’s epithelium. The decrease in lower oesophageal acid exposure decreases inflammation and promotes healing of mucosal defects. This is enhanced by the effects of increased levels of gastrin on cellular migration. These effects are in balance, and appear not to be associated with unwanted side effects of increased proliferation and expansion of the Barrett’s segment. Thus, the beneficial effects of PPI treatment in Barrett’s patients, including symptom control, mucosal healing, and perhaps regression of Barrett’s mucosa prevail. This supports the long-term safety of PPI therapy in Barrett’s patients, but does at the same time not imply that further research is redundant. On the contrary, the available literature data predominantly deals with preclinical endpoints, further studies should focus on endpoints with direct clinical relevance. Some suggestive evidence is coming forward already. An Australian cohort study followed 350 patients with Barrett’s oesophagus for a median 4.7 years. Patients who received PPI maintenance from the time of diagnosis had a subsequent five- to 20-fold decreased risk for development of dysplasia and cancer.6 A similar study from the US followed 236 patients with Barrett’s oesophagus for an average 5 years.7 Use of a PPI after the diagnosis of Barrett’s...
Interleukin-6: a therapeutic Jekyll and Hyde in gastrointestinal and hepatic diseases

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INTRODUCTION

Interleukin-6 (IL-6) was discovered and cloned in 1986. Its receptor IL-6R (CD126) has an unusual organisation, consisting of two proteins: an 80 kDa IL-6 receptor and a 130 kDa signal transducer (gp130). IL-6 and its receptor interact to form a complex consisting of two IL-6 molecules plus two IL-6 receptor proteins and two gp130 proteins. The dimerised gp130 then transduces the signals, a process known as trans-signalling. In addition, a soluble IL-6 receptor also exists and exerts an agonistic effect in complex with IL-6 and can couple with the gp130 to effect transduction. Activation of gp130 leads to activation of JAK kinases and phosphorylation of STAT3, which is translocated to the nucleus and leads to gene expression.1 However, STAT3 also negatively regulates IL-6 signalling by inducing suppressor of cytokine signalling 3 (SOCS3) that in turns inhibits JAK kinase.1

IL-6 is critically involved in both acute and chronic inflammation. At the beginning of acute inflammation, it plays a key role being the main inducer of acute phase reactants such as C-reactive protein, fibrinogen and serum amyloid A protein. When its activity as a proinflammatory cytokine persists, acute inflammation turns into chronic inflammation that includes immune responses. In particular, IL-6 has a detrimental role that favours mononuclear cell accumulation at sites of injury through MCP-1 production, angiogenesis, pro-apoptotic and anti-apoptotic function on T cells and in promoting Th-17 cell differentiation.2 A large number of studies have demonstrated that IL-6 is over-produced in several diseases, and it plays a fundamental role in the pathogenesis of rheumatoid arthritis, asthma, systemic lupus erythematosus, multiple sclerosis, psoriasis, alcoholic hepatitis, viral hepatitis, and in Crohn’s disease and ulcerative colitis, the two major forms of inflammatory bowel disease (IBD).

IL-6 AND IBD

Several lines of evidence suggest that IL-6 is involved in IBD pathogenesis.3 Human studies have reported that IL-6 and IL-6R plasma concentrations are increased in both Crohn’s disease and ulcerative colitis, but no correlation with disease activity exists. Interestingly, increased levels of plasmatic IL-6 might predict clinical relapse in both forms of IBD. In addition, in the inflamed mucosa IL-6 is also up-regulated, as lamina propria mononuclear cells isolated from IBD specimens produce a higher amount of IL-6 compared to controls. In particular, mucosal T cells and macrophages have been shown to be the major source of IL-6 and to activate gp130 positive T cells. IL-6 trans-signalling in turns induces STAT3 activation, which mediates anti-apoptotic signals and increased resistance to death of lamina propria T cells. In experimental colitis IL-6 is mainly involved in the chronic phases of the disease. Recently, the transcription factor NFATC2 has also been demonstrated to be critically involved in IL-6 dependent T cell resistance to apoptosis and activation in experimental colitis, while IFN regulatory factor-4 (IRF4) controls IL-6 production as IRF4 deficient mice are protected from experimental IBD and produce low mucosal

REFERENCES


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Commentaries