

## Leading article

# Proton pump inhibitors for Barrett's oesophagus

Barrett's oesophagus is a metaplastic condition in which the normal squamous oesophageal epithelium is replaced by specialised intestinal metaplasia.<sup>1</sup> Barrett's oesophagus occurs in about 10% of patients with gastro-oesophageal reflux disease (GORD) and predisposes to dysplasia and adenocarcinoma.<sup>2</sup> The incidence of oesophageal and gastric cardia adenocarcinoma is rapidly increasing by a rate exceeding that of any other cancer.<sup>3,4</sup> Over the past decade, acid suppression with proton pump inhibitors (PPIs) has become the mainstay of treatment of patients with Barrett's oesophagus. This article reviews the specific end points of such treatment.

### Control of reflux symptoms

Concomitant symptomatic GORD is common in patients with Barrett's oesophagus and manifests as heartburn, regurgitation, dysphagia, or chest pain.<sup>5</sup> Numerous trials have documented that PPIs provide superior relief of heartburn compared with H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs). In a recent meta-analysis of GORD studies of patients with endoscopically proved erosive oesophagitis, PPIs, irrespective of dose or duration of treatment, provide the greatest overall symptom relief, with 77.4% (10.4%) of patients becoming heartburn-free, which was significantly better than with H<sub>2</sub>RAs (47.6% (15.5%)). Furthermore, PPIs provide faster complete heartburn relief (11.5%/week) than H<sub>2</sub>RAs (6.4%/week).<sup>6</sup> As a group, however, patients with Barrett's oesophagus have greater exposure to oesophageal acid than other patients with GORD<sup>7,8</sup> and control of symptoms may require higher than usual doses of PPIs.<sup>9,10</sup> Even with PPI therapy, however, a subgroup of patients may still have acid regurgitation in spite of control of oesophageal acid exposure.<sup>11</sup> Of note, elderly patients over 65 years of age with Barrett's oesophagus may be much less symptomatic than their younger counterparts and may not require antisecretory therapy.<sup>5</sup>

### Healing of coexistent oesophagitis

Healing of coexistent oesophagitis is an important goal of treatment in patients with Barrett's oesophagus. Elimination of erosive oesophagitis or erythema of the oesophagus permits better delineation of the metaplastic epithelium and facilitates the recognition of dysplasia. Irrespective of dose or length of treatment, healing of oesophagitis is best achieved with PPIs (83.6% (11.4%)) than with H<sub>2</sub>RAs (51.9% (17.1%)). PPIs also achieve faster healing rates (11.7%/week) than H<sub>2</sub>RAs (5.9%/week).<sup>5</sup>

### Prevention of recurrence of oesophagitis

In many patients GORD is a chronic disease with 50–80% of patients relapsing within six to 12 months after healing of oesophagitis and discontinuation of treatment. Patients with Barrett's oesophagus as a group are more likely to have recurrences because they have severe physiological abnormalities, such as low lower oesophageal sphincter tone, impaired oesophageal body peristalsis, and greater

than average oesophageal acid exposure.<sup>7</sup> After initial healing of oesophagitis, maintenance PPI therapy prevents relapses in more than 80% of patients with GORD.<sup>12–14</sup>

### Healing of oesophageal ulcers

In patients with Barrett's oesophagus, ulcers are located either within the metaplastic columnar mucosa, typically in the lower part of the oesophagus, or higher up in the distal portion of the squamous oesophagus near the squamo-metaplastic junction. Regardless of their location, these ulcers cause reflux symptoms in 70% of cases and may contribute to anaemia and gastrointestinal bleeding in 50%. PPIs heal these ulcers in 80–90% of cases, but recurrences are common.<sup>15</sup>

### Prevention of stricture formation

Long term PPI therapy is often necessary to prevent peptic stricture formation, which may occur in up to 70% of Barrett's ulcers at the squamo-metaplastic junction. In a prospective randomised double blind trial comparing omeprazole (20 mg daily) with ranitidine (150 mg twice daily) in patients with reflux induced peptic strictures, 65% of patients treated with omeprazole were asymptomatic, compared with 43% treated with ranitidine.<sup>16</sup> Similar improvement in clinical outcome in patients with oesophageal strictures occurs with other PPIs as well. Another multicentre, randomised controlled trial showed that treatment with lansoprazole (30 mg daily) resulted in fewer dilatations and more dysphagia-free patients than high dose ranitidine (300 mg twice daily).<sup>17</sup>

### Regression of Barrett's metaplastic surface

Regression of the metaplastic surface is considered an important end point in the management of patients with Barrett's oesophagus. The risk of malignant transformation in Barrett's oesophagus should be related, at least in part, to the extent of its mucosal involvement.<sup>18,19</sup> The greater the length of tubular oesophagus occupied by intestinal metaplasia, the higher the number of predisposed cells undergoing molecular or genetic changes leading to dysplasia and adenocarcinoma. By contrast, a reduction in the surface or complete regression of intestinal metaplasia would reduce or eliminate the risk of malignancy. To this end PPIs have been used either alone or in combination with an ablative endoscopic modality (see later). Over the past decade, several studies using various PPI regimens as single therapy for variable time periods have yielded inconsistent results.<sup>20–25</sup> In these trials, 320 patients treated with either omeprazole (20–40 mg orally once or twice daily) or lansoprazole (30–60 mg orally once or twice daily) for six to 72 months exhibited a 0–54% (mean, 13%) reduction in length and 0–21% (mean, 10%) reduction in surface of Barrett's oesophagus. However, measurement of the surface and length of Barrett's oesophagus is prone to bias

**Abbreviations used in this article:** DGOR, duodenogastro-oesophageal reflux; GORD, gastro-oesophageal reflux disease; H<sub>2</sub>RA, H<sub>2</sub>-receptor antagonist; PPI, proton pump inhibitor.

and error because it is influenced by peristalsis, the presence of sliding hiatal hernia, inter- and intra-observer variability, and inherent problems with photodocumentation. Furthermore, control of the intraoesophageal pH and duodenogastro-oesophageal reflux (DGOR) has been inadequately documented, and the frequency and duration of PPI therapy are variable.

The prospective, double blind randomised study by Peters and colleagues<sup>26</sup> in a recent issue of *Gut*, is the latest effort aiming at reducing the length of Barrett's metaplasia using pharmacological acid suppression with 40 mg oral omeprazole twice daily for two years. The authors show a statistically significant regression of the Barrett's epithelium both in terms of length (-4.8%/month (95% confidence interval (CI) -11.6 to -0.8)) and surface (-9%/month (95% CI -15 to -3)), attributed to complete normalisation of the intraoesophageal pH. Although these results are consistent with some previous studies,<sup>21 22</sup> their clinical importance at this point is questionable. Nevertheless, it is possible that the two year observation period is inadequate to allow full re-development of squamous epithelium and more time would be needed.

### Promotion of appearance of squamous islands

Most (50–90%) patients with Barrett's oesophagus treated with PPIs develop squamous islands within the Barrett's surface.<sup>21 24</sup> These islands may reflect a true regression of the metaplastic epithelium or merely a superficial change with persistence of underlying intestinal metaplasia. Over time, these islands may coalesce and involve a major portion of the Barrett's mucosa thereby reducing its overall surface. Unless complete replacement of Barrett's epithelium by squamous epithelium occurs, endoscopic surveillance is still necessary. Furthermore, because more than one third of biopsy samples of macroscopic squamous islands contain microscopic intestinal metaplasia, the importance of these islands of squamous oesophageal re-epithelialisation is not clear and longer follow up of a larger number of patients will be necessary.<sup>26</sup>

### Reduction of duodenogastro-oesophageal reflux

The composition of refluxed material is important in Barrett's oesophagus. Although acid reflux is the primary factor in the development of metaplasia, bile reflux tends to parallel acid reflux and may have a synergistic role. There is increased evidence that Barrett's oesophagus and adenocarcinoma are related to DGOR rather than acid reflux.<sup>27</sup> The best way of decreasing DGOR is an antireflux operation that corrects the defective lower oesophageal sphincter. However, aggressive acid suppression therapy with omeprazole 20 mg orally twice daily increases gastric pH, decreases gastric volume, and diminishes DGOR to a similar degree to antireflux surgery.<sup>28</sup> However, experimental and clinical data also suggest that acid suppressive therapy may be harmful to patients with Barrett's oesophagus by allowing continued and uninhibited DGOR.<sup>29</sup>

### Management of dysplasia

Intensive antireflux therapy with PPIs is generally instituted when low grade dysplasia is found in order to minimise oesophageal inflammation that may confound pathological interpretation. Usually, after eight to 12 weeks of such intensive therapy, endoscopic examination is repeated to obtain oesophageal biopsy and cytology specimens. Ideally, PPI therapy should be titrated to effective (complete) intraoesophageal acid suppression.<sup>10</sup> If dysplasia is found again, intensified surveillance every six months is warranted. Although most patients with high grade dysplasia

are also treated with PPIs, oesophageal resection or other endoscopic ablation modalities are used in order to arrest progression to invasive cancer (see later).

### Prevention of dysplasia or adenocarcinoma

The maintenance of normal epithelial differentiation and proliferation is an important goal in cancer chemoprevention. In ex vivo studies, continuous exposure of Barrett's oesophageal explants to acid induces differentiation and reduces proliferation, whereas short pulses of acid exposure increase proliferation. Effective intraoesophageal acid suppression with lansoprazole favoured differentiation and decreased proliferation over a six month period, supporting the hypothesis that effective intraoesophageal acid suppression may be beneficial in the long term management of patients with Barrett's oesophagus by allowing for more differentiated epithelia while minimising cell proliferation.<sup>30</sup> Theoretically, this new Barrett's metaplastic phenotype would be less likely to progress to dysplasia or adenocarcinoma. This point however has not yet been proved clinically as none of the studies of PPI therapy in Barrett's oesophagus had an impact on regression of dysplasia.<sup>31</sup> Nevertheless, the limited number of patients with dysplasia enrolled in such trials and possibly the short duration of study do not provide firm conclusions on the impact of PPI induced reduction in cell proliferation and increase in cell differentiation or on the development of dysplasia.

### Adjuvant treatment to ablation modalities

Because of the failure of medical and surgical therapy to reverse Barrett's oesophagus, PPI therapy has been used in combination with endoscopic ablation. As long as acid reflux is controlled with PPIs, it is possible to ablate the metaplastic and dysplastic columnar epithelium of Barrett's oesophagus using thermal<sup>32</sup> or photochemical energy<sup>33</sup> and permit regeneration of squamous mucosa.

### Summary

PPIs are the most important pharmacological agents in the management of patients with Barrett's oesophagus as they control symptoms, heal ulcers, and prevent strictures. The impact of PPI therapy on the natural history and evolution of Barrett's oesophagus towards dysplasia and adenocarcinoma is unclear and further long term studies that control for intraoesophageal acid and bile reflux will be necessary.

G TRIADAFILOPOULOS

Professor of Medicine,  
Stanford University School of Medicine,  
Chief, Gastroenterology Section (111-GI),  
Veterans Affairs Palo Alto Health Care System,  
3801 Miranda Avenue,  
Palo Alto, CA 94304, USA  
email: vagt@leland.stanford.edu

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