Proton pump inhibitors (PPIs) are commonly used to treat patients with GERD, but many patients do not experience symptomatic relief, despite long-term therapy. However, acid pocket formation during the post-prandial period has recently been identified as the primary mechanistic driver of acid reflux in patients with GERD. Following on from this discovery, there is clinical evidence to suggest that specifically targeting the acid pocket with alginate-antacid formulations (such as Gaviscon Advance) is an effective method of reducing GERD symptoms and improving patient quality of life.

**GERD: An emerging therapeutic challenge in Hong Kong**

GERD is a chronic disease resulting from the stomach contents regularly flowing back into the oesophagus. The gastric acid present in the reflux leads to symptoms such as heartburn and acid regurgitation, which impairs patient quality of life and reduces productivity. In severe cases, acid can accumulate in the oesophagus leading to complications, such as oesophagitis, stricture and Barrett’s oesophagus.

Historically, GERD was considered to be primarily a Western disease (prevalence: 8.8–25.9%) and uncommon in Asia (prevalence: 8.9% in Hong Kong and 2.5–7.8% across East Asia). However, there is evidence to suggest that the prevalence of GERD in Asia is increasing, so developing therapeutic strategies for maintaining remission amongst Asian patients will be important for minimizing GERD-related burden of disease.

**Current treatment strategies for GERD**

Conventional therapies for GERD include long-term PPI therapy or laparoscopic anti-reflux surgery (LARS). Both therapies demonstrate similar efficacy with one clinical trial reporting 5-year remission rates of 92% and 85% for patients assigned to PPI therapy (n=192) or LARS (n=180), respectively. While surgery significantly reduces reflux, the majority of patients still rely on medical intervention post-surgery, such as PPI therapy, because post-operative dysphagia, bloating and flatulence is common. However, despite PPI therapy often being a first-line treatment in GERD, PPI therapy has limited efficacy, with up to 45% of patients taking PPIs remaining symptomatic.

**Asian patients are significantly less likely than Western patients to respond to PPI therapy.** However, this outcome may have been confounded by relative disease severity, as Asian patients typically presented with a more severe disease profile, including non-erosive reflux disease (NERD) and severe tissue erosion. Furthermore, concern has been raised over the long-term risks associated with PPI therapy. Chronic PPI administration is associated with an increased risk of fractures, Clostridium difficile colitis and possible drug-drug interactions in patients with a history of an acute coronary syndrome prescribed clopidogrel. These unmet needs provide the basis for identifying alternative therapeutic options for patients with GERD that avoid chronic PPI therapy.

**The acid pocket: A novel therapeutic target in the treatment of GERD**

Given the often inadequate therapeutic response of patients with GERD to PPIs, there is a need to identify novel mechanisms involved in the pathophysiology of GERD that could be targets for new therapeutic strategies. For example, there is emerging evidence that an acid pocket forming as a result of the non-homogenous distribution of gastric contents during the post-prandial period contributes to post-prandial acid reflux in patients with GERD. While most of the distal stomach gastric acid is buffered by food, which is facilitated by peristaltic motility, the proximal stomach remains relatively immotile during this period, thereby promoting the accumulation of acidic

**Figure 1**

A post-prandial acid pocket forms in the stomach of healthy patients. The acid pocket is longer and can lead to more acid reflux in patients with a large hiatus hernia.
gastric secretions at the gastroesophageal squamocolumnar junction, forming an acid pocket.\textsuperscript{14} While the acid pocket is a typical phenomenon during the post-prandial period in all individuals, in patients with GERD or a hiatus hernia the acid pocket is longer and can extend through the oesophagogastric junction (Figure 1).\textsuperscript{16,17} Similarities in pH have been found between the oesophageal refluxate and the acid pocket, suggesting the acid pocket is likely the source of post-prandial acid reflux in patients with GERD.\textsuperscript{15} Therefore, the acid pocket represents a unique therapeutic target for the treatment of GERD.

Alginate-antacid formulations specifically target the acid pocket to provide a barrier against acid reflux

Alginate-antacid formulations have demonstrated target specificity by accumulating at the acid pocket. As alginate-antacid formulations contain a polysaccharide polymer, they form a gel upon exposure to the low pH environment of the acid pocket.\textsuperscript{18} By incorporating sodium bicarbonate into the formulation, carbon dioxide is liberated when the gel forms and is trapped in the gel matrix, causing the gel to float above the acid pocket, forming a ‘raft’ (Figure 2).\textsuperscript{18} This raft subsequently displaces the acid pocket below the diaphragm, providing a physical barrier against regurgitation.\textsuperscript{19}

Alginate as an add-on therapy in non-responsive GERD patients

A double-blind, randomized, placebo-controlled trial has assessed the efficacy of Gaviscon Advance as an add-on therapy in patients who have not responded to PPI therapy (Figure 3).\textsuperscript{20} At 7 days following treatment initiation, changes in heartburn reflux dyspepsia questionnaire (HRDQ) scores were significantly greater for patients randomly assigned to receive PPI therapy in conjunction with Gaviscon Advance versus placebo (Figure 3).\textsuperscript{20} Additionally, Gaviscon Advance as an add-on therapy significantly reduced the frequency of heartburn, overall reflux and night-time symptoms compared with placebo (Figure 3).\textsuperscript{20} The Gaviscon Advance alginate-antacid formulation was well-tolerated with no difference in adverse events being reported between study arms. Collectively, these findings suggest that the Gaviscon Advance alginate-antacid formulation is an effective adjunct to PPI therapy for patients with GERD.

Conclusion

The identification of the acid pocket in the proximal stomach as the origin of acid reflux has led to the emergence of novel therapies that selectively target this region. The unique raft-forming mechanism of action of alginate-antacid formulations has proven efficacy in specifically targeting the acid pocket to reduce the symptoms of GERD and improve patient quality of life. Collectively, these data suggest that the Gaviscon Advance alginate-antacid formulation is an effective adjunctive therapy for patients who are only partially responsive to PPI therapy, reducing the need for multiple dosing with PPI inhibitors.