Proton pump inhibitor non-responsive gastroesophageal reflux disease: unraveling an enigma?

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Gastroesophageal reflux disease (GERD) affects 10–20% of adults in Western countries (1,2) and 13% of Americans use medications for GERD at least twice weekly (3). In the USA alone, it is estimated that the annual direct and indirect costs incurred due to GERD is approximately $10 billion (4).

Proton pump inhibitors (PPIs) have been the gold standard treatment of GERD for over two decades. In multiple studies, PPIs have been shown to be superior over placebo and histamine-2 receptor antagonists for the control of symptoms, esophageal mucosal healing, and improvement in quality of life (2). However, despite this success, it has been estimated that approximately 10–40% of patients with GERD do not respond adequately to PPIs in standard doses (1,4). Recently, more attention has been focused on these PPI non-responsive (PPINR) patients and how best to treat them. PPI non-responsive GERD is typically defined as patients who have objective evidence of reflux (either esophagitis or abnormal pH study) despite at least 8-week trial of PPI therapy (2,4,5). Due to sparse evidence of the effectiveness of adjunctive therapies, there is no standard diagnostic or treatment approach to patients with PPINR GERD, which has created a sea of confusion and patients often getting referred to surgical anti-reflux procedures.

In a recent issue of the *Diseases of the Esophagus*, Hillman *et al*. present a narrative review of medical therapy options for PPINR GERD (6). They divide their review into two main segments: (I) the efficacy of CYP independent *vs*. CYP dependent PPIs in participants with different metabolizing potential; and (II) the efficacy of medications in addition to PPIs in the treatment of GERD. Hillman *et al*. should be praised for their meticulous work on this subject.

The authors reviewed 13 studies that compared the efficacy of PPIs based on subject's CYP metabolization genotype (6). Subjects that were homozygous for the rapid CYP2C19 metabolizer gene were known as the homozygous extensive metabolizer (homoEM) group, while the ones with slower CYP2C19 metabolizer gene were characterized as the poor metabolizer (PM) group, and patients with one of each gene comprised the heterozygous extensive metabolizer (heteroEM) group. In the five studies that compared the effects of the more CYP-dependent PPIs (lansoprazole, pantoprazole, and omeprazole) on subjects based on their genotype, the poor metabolizers generally had better outcomes, with both better symptomatic relief and higher rates of remission of erosive esophagitis, as compared to the heteroEM and homoEM groups. The heteroEM group also fared better compared to the homoEM group. The differences between the groups were no longer significant in the one study where the PPI dosing was increased to twice a day (6).

Six other studies compared the efficacy of the more CYP-independent PPIs (rabeprazole and esomeprazole) among the different genotypes and found that the symptom relief and erosive esophagitis healing rates were not significantly different (6). Lastly, when comparing response between CYP2C19 dependent and independent PPIs, evidence was conflicting with one study showing that

resolution of symptoms at 4 weeks did not differ across genotypes, while another showing decrease recurrence rate in patients treated with rabeprazole compared to CYP-dependent PPIs (omeprazole or lansoprazole) (6). Studies have shown that for symptom relief, esomeprazole (CYP-independent PPI) is more rapidly effective compared to CYP dependent PPIs such as omeprazole (7,8), lansoprazole (9,10), and pantoprazole (11). Two meta-analyses have shown that esomeprazole was superior to omeprazole and other PPIs for healing esophagitis at four and 8 weeks (12,13). However, these studies primarily included patients that were treatment naïve and did not evaluate patients with PPINR GERD.

When reviewing the benefits of adjunctive medications in the treatment of GERD, Hillman *et al*. found mixed results. The authors specifically reviewed 27 studies that analyzed multiple other medical therapies in conjunction with PPI use. Histamine-2 receptor antagonist (H2RA) use in addition to PPI did decrease nocturnal acid breakthrough and nighttime as well as overall symptoms compared to PPI use alone, but many subjects experienced tachyphylaxis and stopped taking H2RAs, limiting the clinical applications (6).

Studies analyzing adjunctive promotility agents (mosapride, prucalopride, revexepride, and domperidone) were also reviewed (6). Among all GERD patients, mosapride showed no differences compared to PPI monotherapy, however, in the PPI non-responsive group specifically, symptoms improved with mosapride plus PPI (6). Prucalopride was only studied in a case report of four subjects with constipation and GERD and did show improvements in symptoms. Revexpride + PPI, on the other hand, did not show any improvements in symptoms compared to PPI monotherapy among PPINR participants (6). Domperidone + PPI was helpful in providing symptom relief while patients were on the medications, but differences between the groups disappeared post-treatment (6). In a previous randomized, placebo-controlled trial, metoclopramide and domperidone did not improve duration of esophageal acid exposure or clearance despite both agents significantly increasing the lower esophageal sphincter pressure (14).

Finally, mucosal protective agents (rebapamide, irsogladine, and mirgeal) in addition to PPIs showed some benefit compared to PPI alone (6). Rebapamide + PPI reduced symptom recurrence rate of EE that had been treated with PPIs (6). Irsogladine + PPI did not show improvements in symptoms across all groups but did show improvement over PPI alone in a subgroup of NERD patients without microscopic changes on biopsy. Mirgeal also demonstrated improved symptom control with PPI in patients with NERD (6).

This study has several limitations. First, this systematic review included studies that enrolled participants irrespective of how the diagnosis of GERD was made (including self-reported symptoms or patient reported questionnaires). As the authors acknowledged, this was due to paucity of studies with clearly defined objective evidence of PPI refractory GERD, but regardless, it increases risk of potentially including patients that might have been misclassified as GERD. Second, studies comparing the efficacy of CYP independent and dependent PPIs draws mainly from studies conducted in Japan and Taiwan. Only one of the 13 studies reviewed was conducted in Europe and there were no studies from the United States. Given higher prevalence of rapid metabolizers (homoEM) among Caucasians (59.7–69.9%) compared to Asian populations, one would expect greater benefit with CYP independent PPIs in the Western population (15). Third, studies evaluating efficacy of CYP polymorphism on PPI effectiveness were primarily studied in patients with severe reflux (erosive esophagitis). Evidence behind using this approach among patients with non-erosive reflux disease (NERD) is unclear. Finally, evidence of other pharmaceutical options is lacking as noted by the authors due to lack of uniform studies (including medication dosing, follow-up period, and the method by which the diagnosis of refractory GERD was made). We propose the following algorithm (*Figure 1*) in patients with PPINR GERD based on current literature with most important delineation being testing to prove objective evidence of reflux. The current American College of Gastroenterology (ACG) guidelines recommend that patients with low pre-test probability (atypical presentation without concomitant heartburn or regurgitation) of reflux be tested OFF medication with pH or multi-channel intraluminal impedance-pH (MII-pH), while those with high pre-test probability (typical symptoms of heartburn/regurgitation or partial response to PPI) of reflux be tested with MII-pH ON therapy (2). If ambulatory reflux testing is negative, then further work-up should be focused towards identifying alterative etiology given nearly 35% of patients with symptoms of GERD in one study had an alternative diagnosis on further evaluation (5.5% had eosinophilic esophagitis, 8.3% had achalasia or another dysmotility disease, 16% had functional heartburn,

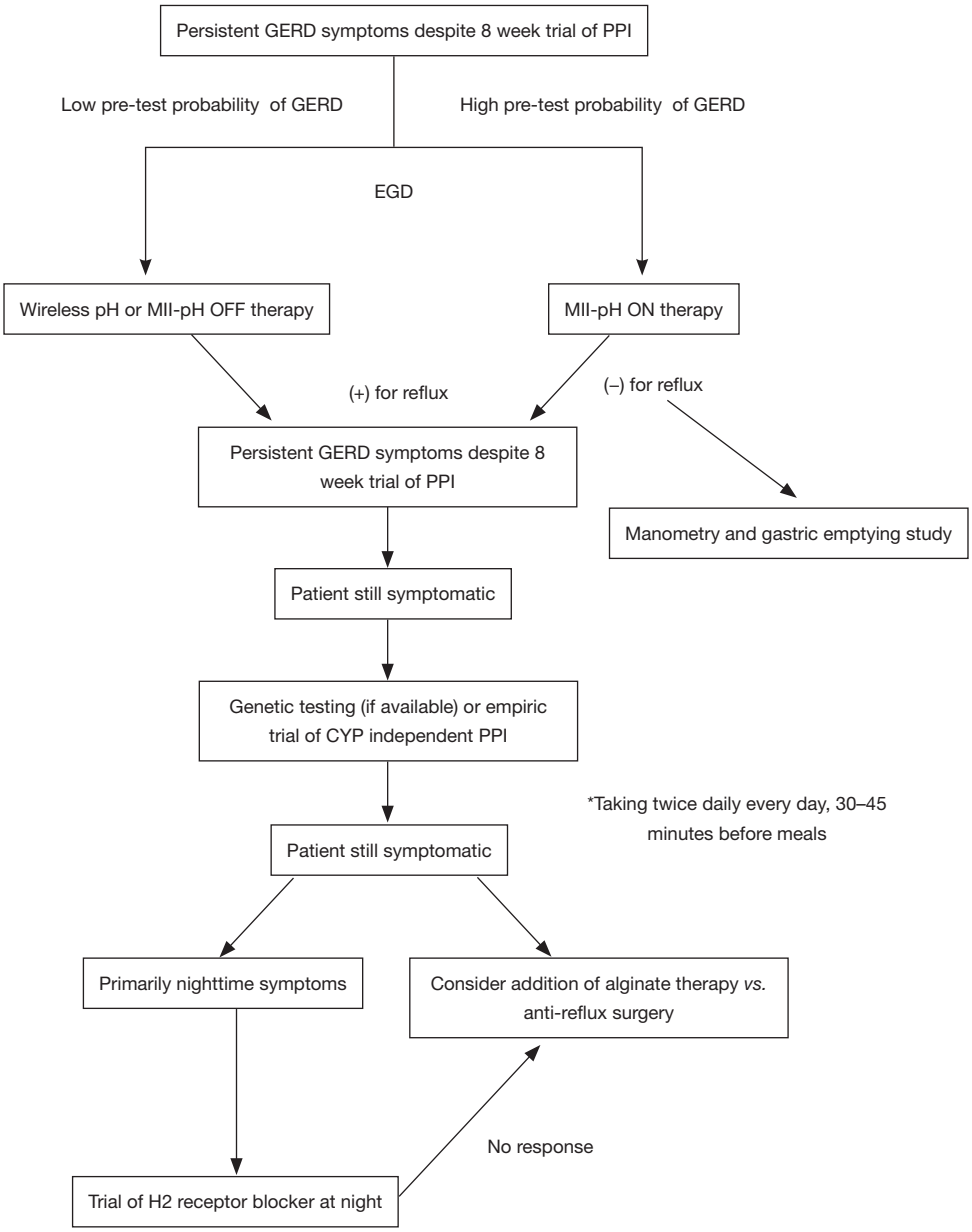

Figure 1 Proposed algorithm for evaluation and management of patients with persistent esophageal or extra-esophageal reflux symptoms despite trial of proton pump inhibitor therapy. PPI, proton pump inhibitor; EGD, esophagogastroduodenoscopy; MII-pH, multi-channel intraluminal impedance-pH; GERD, gastroesophageal reflux disease; CYP, cytochrome p450.

and 5.8% had gastroparesis) (5).

Hillman *et al.* (6) have made an important contribution in highlighting the current evidence behind treatment for patients with PPI non-responsive GERD. More importantly, this study reminds us that our current literature critically lacks high-quality outcomes based studies in this difficult to treat group.

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