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TOPIC HIGHLIGHT

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Proton pump inhibitor resistance, the real challenge in gastro-esophageal reflux disease

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Abstract

Gastro-esophageal reflux disease (GERD) is one of the most prevalent chronic diseases. Although proton pump inhibitors (PPIs) represent the mainstay of treatment both for healing erosive esophagitis and for symptom relief, several studies have shown that up to 40% of GERD patients reported either partial or complete lack of response of their symptoms to a standard PPI dose once daily. Several mechanisms have been proposed as involved in PPIs resistance, including ineffective control of gastric acid secretion, esophageal hypersensitivity, ultrastructural and functional changes in the esophageal epithelium. The diagnostic evaluation of a refractory GERD patients should include an accurate clinical evaluation, upper endoscopy, esophageal manometry and ambulatory pH-impedance monitoring, which allows to discriminate non-erosive reflux disease patients from those presenting esophageal hypersensitivity or functional heartburn. Treatment has been primarily based on doubling the PPI dose or switching to another PPI. Patients with proven disease, not responding to PPI twice daily, are eligible for anti-reflux surgery.

Key words: Gastro-esophageal reflux disease; Proton pump inhibitor; Ambulatory pH-impedance monitoring; Esophageal hypersensitivity; Gastro-esophageal reflux disease treatment

Core tip: The present review focuses on the subgroup of patients in whom proton pump inhibitor refractoriness more frequently occurs, on the mechanisms possibly involved in the lack of response, the diagnostic work-up and the therapeutic strategies in these patients. Various mechanisms and factors have been demonstrated and some mechanisms have also been proposed, although not yet supported by strong evidence. In the management of these patients, a careful clinical interview might conduct the diagnostic evaluation and the therapeutic approaches.

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INTRODUCTION

Gastro-esophageal reflux disease (GERD) is one of the most prevalent chronic diseases in Western countries, affecting approximately 20% of the United States adult population weekly, and 7% daily[1,2]. Although the acid-suppressive drugs have improved in efficacy over the last few decades, and proton pump inhibitors (PPIs) represent the mainstay of treatment both for healing erosive esophagitis and for symptom relief as well as for preventing complications, several studies have shown that up to 40% of GERD patients reported either partial or complete lack of response of their symptoms to a

standard PPI dose once daily[3-5]. Therefore, particularly in third referral Gastrointestinal Units, the management of refractory GERD patients is a very common, as well as a very challenging, task. Indeed, chronic heartburn is associated not only with a significant decrease in all the physical and mental domains of health-related quality of life questionnaires but, also, with a significant increase in healthcare costs, due to repeated diagnostic procedures, physician examinations and drug prescriptions[6]. The present review focuses on the subgroup of patients in whom PPI refractoriness more frequently occurs, on the mechanisms possibly involved in the lack of response, the diagnostic work-up and the therapeutic strategies adopted in these patients.

MOST DIFFICULT PATIENTS

The clinical suspicion that the symptomatic response to PPIs is less frequent in those patients affected by the most common presentation of GERD, *i.e.*, non-erosive reflux disease (NERD), than in those presenting erosive esophagitis (ERD) has been confirmed several years ago. In one of the first reports focusing on NERD patients, treatment with omeprazole 20 mg for 4 wk resulted in complete symptom relief in only 46% of patients, in even fewer of them on 10 mg and in those receiving placebo, and symptom improvement (satisfaction) in 66%[7]. The main messages of the study were the better results obtained with higher doses, which do not support the concept of NERD as a milder form of GERD and, more important, the concept that symptom relief proves to be directly correlated with esophageal acid exposure time, that is to say, the greater the acid exposure, the higher the PPI response. So far, only a few trials have compared the outcome of PPI treatment in NERD *vs* ERD patients. Almost all of these trials were carried out using a double blind, parallel group design with a short (4 wk) follow-up period. In a study performed by Bate *et al*[8], relief of heartburn was achieved in 47% of NERD, and in 53% of ERD patients (the difference not being significant). Of interest, as far as concerns the non-responders, 67% became heartburn-free after an additional 4 wk of treatment[8].

Better results, both in NERD and ERD patients, have been reported in a multicenter study by Venables *et al*[9]: heartburn relief, was achieved after 4 wk of omeprazole, in more than 60% of NERD and in 79% of ERD patients. Galmiche *et al*[10], besides heartburn remission, reported semi-quantitative measures of symptom severity and their impact on quality of life: At 4 wk, heartburn was resolved in 62% of NERD and 71% of the ERD patients, even higher values being observed after an additional 4-wk treatment with omeprazole. Of interest, quality of life improved in all treatment groups, but the improvement was higher in those on full PPI dose (*vs* half-dose) group[10]. Armstrong *et al*[11], in a randomized, Canadian multicenter study, confirmed complete relief in a larger proportion (although not significant) of ERD, than NERD, patients receiving pantoprazole. Although some data were not stratified for the presence/absence of esophagitis, a modified intention-to-treat analysis demonstrated, in the PPI group, a trend of increased therapeutic gain throughout the 4 wk[11]. More recently, a multicenter trial performed in Japan, has shown that, following 4-wk rabeprazole 40 mg/die, complete relief of symptoms was achieved in only 36% of the NERD and in approximately 55% of the erosive group, a response rate similar to that observed in Western countries. Here, patients were stratified according to a modified Los Angeles classification and, of interest, the more severe the esophageal mucosal injury, the more effective the therapy. The design of the study and symptom assessment could also demonstrate that the median time to the first 24- and 48-h heartburn-free intervals was significantly shorter for erosive than for non-erosive patients[12]. Before concluding the issue regarding the response to PPI treatment in non-erosive *vs* erosive reflux disease, it may be useful to re-consider a major dilemma concerning NERD, namely the lack of a standard definition, which is likely to affect the results of clinical trials, and makes interpretation of data, challenging. It is generally agreed that NERD is the most common presentation (up to 75%) of GERD, with the same symptom severity and quality of life impairment as ERD, but, at the same time, there is still lack of agreement concerning the definition of NERD: should all symptomatic patients with endoscopy-negative findings be considered to be suffering from NERD? The 24-h pH test does, indeed, distinguish patients with and without pathological esophageal acid exposure, and, more important, patients with and without significant symptom-reflux association, which can reveal hypersensitivity to non-pathological acid exposure.

Endoscopy-negative patients not presenting pathological acid exposure, with negative symptom-reflux association and without a satisfactory response to the PPI test are, indeed, affected by functional heartburn, according to the Rome Ⅲ criteria, and thus do not belong to the NERD population. These "functional" patients, in whom symptoms are, by definition, not related to reflux, might be a minority but they frequently attend the outpatients units and are, often, enrolled in clinical trials. The low response to PPIs reported in NERD may be affected by including this functional subgroup in a "too heterogeneous" NERD population. Another common risk of mis-classification of NERD is due to the healing of esophagitis at the time of upper endoscopy, and, thus, a recent consensus underlines the importance not only of an appropriate pharmacological washout before endoscopy but, also, of checking for previous endoscopic findings in the same patient, if available[13]. In the attempt to better evaluate the response rate in NERD patients according to the different criteria of the participants enrolled in clinical trials, a recent meta-analysis of the literature has demonstrated that lower rates of partial or complete response are reported in the large majority of studies with a poor characterization of the patients, lacking pH-test findings

Table 1 Principal mechanisms and factors involved in proton pump inhibitor resistance

Adherence to PPI therapy
Compliance
Dosing, time
Reflux pattern
Weakly acidic reflux
Proximal reflux
Mixed reflux
Residual acid refluxes
Esophageal hypersensitivity
Other mechanisms
Reduced PPI bioavailability
Increased PPI metabolism
Mutations cyt. p450

PPI: Proton pump inhibitor.

and, therefore, likely including patients with functional heartburn and functional dyspepsia[14]. Future studies, enrolling well-defined NERD patients and, hopefully, with a longer follow-up, might offer more precise data on PPI efficacy.

MECHANISMS AND FACTORS INVOLVED IN PPI RESISTANCE

In patients with reflux symptoms refractory to medical therapy, namely those with typical GERD symptoms - heartburn and regurgitation - not responding to a standard or double dose of PPI given for at least 8 wk, various causes have been demonstrated and some mechanisms have also been proposed, although not yet supported by strong evidence. Principal mechanisms and factors involved in PPI resistance are summarized in Table 1.

Ineffective control of gastric acid secretion, in terms of excessive residual acid reflux despite adequate PPI treatment, can be due to lack of compliance, rapid PPI metabolism - due to CYP2C19 polymorphism - or hypersecretory syndromes such as Zollinger Ellison. While these two latter conditions are uncommon, non-compliance to treatment, in terms of incorrect medication dose or timing, is reported to frequently occur. Two recent meta-analyses have clearly shown that lack or non-compliance to therapy is particularly frequent in GERD patients, in whom adherence to the prescribed PPI is acceptable in only 55% of patients, at one month, and in 30% at 6 mo after prescription.

The lowest levels of compliance, in terms of daily or dose administration, were observed in NERD patients, and, of the various factors, the most frequently reported were: lack of knowledge about the treated disorder, desire for personal control, side-effects and additional medications[15]. In a study focusing on patients with persistent GERD symptoms despite prolonged PPI treatment, it was reported that in less than 46% of these patients the drug was administered in the fasting state, before breakfast[16].

In the new era of combined pH and impedance 24-h monitoring, it is possible to detect reflux episodes with more accuracy compared to the pH-monitoring alone, following the movement of refluxate along the esophageal body and to distinguish air/liquid component as well as acidic composition of each episode. Over the last decade, several pH-impedance investigations have been conducted on patients with NERD and, particularly, on those patients with a poor symptomatic response to PPIs. Results emerging from those studies have confirmed a condition already observed with pH-tests, namely esophageal hypersensitivity in terms of perception of not-abnormal reflux, and this enhanced sensitivity involves not only acidic reflux but, also, weakly acidic reflux and gas-containing (mixed) reflux episodes. Either cohort studies analyzing the reflux pattern and reflux-symptom association[17] or pathophysiologic investigations, looking at the perception of each reflux episode[18] have clearly shown that, in NERD patients, besides acidic reflux, weakly acidic reflux and gas-containing episodes (both of them probably associated with increased reflux volume and esophageal distension) are responsible for a significant proportion of symptoms (approximately 20%), much higher when compared to those in ERD patients. These studies have demonstrated both a possible mechanism explaining symptom persistence despite acid suppression and the higher diagnostic yield of the pH-impedance test in these patients.

Recent pathophysiological investigations have also shown that a dynamic characteristic, such as the proximal migration of reflux, an indicator of high volume refluxate, represents a major determinant of reflux perception, particularly in NERD patients. Interestingly, in large multicenter studies, these three characteristics, namely weakly acidic reflux, mixed (liquid-gas) reflux and the higher proximal extent, have also been recognized as the main mechanisms underlying failure of PPI treatment in patients with reflux-related symptoms[19-21]. Finally, experimental studies suggest that some of the NERD patients presenting PPI-resistance may also present a more generalized condition of visceral hyperalgesia[22].

The research field focusing on the ultrastructural and functional changes in the esophageal epithelium has contributed to a better understanding of NERD and of PPI-resistance pathophysiology. In those conditions not associated with severe mucosal inflammation and/or epithelial erosions, it is not clear how severe and recurrent symptoms can occur in an apparently normal mucosa (NERD). A well studied ultra-structural alteration, *i.e.*, dilated intercellular spaces (DIS), has been demonstrated by means of Transmission Electron Microscopy both in ERD and NERD patients[23,24], and this would explain the genesis of symptoms triggered by the activation of intramucosal chemo-sensitive pain-receptors. The increased para-cellular permeability, associated with the presence of DIS, and the resulting breakdown in the epithelial barrier, do not necessarily result from excessive acid exposure, as shown in NERD patients presenting a normal acid contact time at pH-monitoring, can be induced, in ex-

perimental models, by weakly acidic and acidified bile solutions and even occurs during acute stress situations[25]. Interestingly, the feature of DIS has been observed in patients with PPI-resistant symptoms, during treatment, but not in patients affected by functional heartburn[26], returns to normal following PPIs, together with symptoms[27], and, therefore, the impaired mucosal integrity would now appear to be the mechanism that best explains the enhanced sensitivity to chemical and mechanical stimulation in NERD and PPI-resistant patients. Indeed, peripheral sensory pathways, in terms of up-regulated pain receptors, central sensitization of sensory neurons and processing of ascending stimula are now under intense investigation and may be involved in the conditions of esophageal and visceral hypersensitivity.

Several conditions not, or not directly, related to gastro-esophageal reflux, should also be considered when assessing PPI refractoriness. Infectious esophagitis, eosinophilic esophagitis and pill esophagitis may be other, not frequent, causes of refractory heartburn. Anxiety and depression, demonstrated to increase reflux perception, may also be involved.

DIAGNOSTIC EVALUATION

Clinical evaluation

As previously pointed out, lack of compliance - in terms of adherence to treatment, timing and dosing - and the presence of functional heartburn are the main findings in patients referred for refractory heartburn, therefore a careful interview, also looking at the confounding presence/co-existence of atypical - ENT and respiratory - symptoms and at their possible relation with GER, is crucial. The presence of functional disorders, such as functional dyspepsia and irritable bowel syndrome, as well as of psychological disorders, should also be assessed as these are associated with visceral hyperalgesia as well as a with reduced response to acid-suppressive drugs.

Endoscopy

Although the sensitivity of upper endoscopy is very low - most patients have NERD - it might be helpful for ruling out pill and infectious esophagitis, eosinophilic esophagitis (4%-6% in PPI-refractory patients, multiple biopsies should be obtained) and the rare cases of Zollinger Ellison syndrome.

Esophageal manometry

Conventional or high-resolution manometry should be performed in order to rule out severe motor disorders, to better locate LES for pH-sensor positioning, and, furthermore can provide useful information when a surgical anti-reflux approach is indicated.

Ambulatory pH [impedance] monitoring

The only test which provides quantitative information on the esophageal exposure to reflux, also assessing its relationship with symptoms, remains 24-h ambulatory pH-monitoring. Prolonged (48 to 96 h) wireless pH-monitoring improves the diagnostic yield of the test by improving the likelihood of a positive reflux-symptom association[28]. We have previously discussed the advantages of the combined ambulatory pH-impedance test, as well as its greater accuracy in discriminating NERD patients from those presenting esophageal hypersensitivity or functional heartburn. Indeed, typical and atypical symptoms not responding to PPIs represent the main indication for performing ambulatory pH-impedance monitoring. The test performed "off" therapy can confirm or exclude a pathological gastro-esophageal reflux and, according to a recent investigation[29] offers the best chances to detect a positive association between symptoms and reflux episodes. Recent studies have shown that refractory patients studied "off" and "on" therapy are, indeed, characterized by an abnormal number of reflux events and a higher sensitivity to all types of reflux - acidic, weakly acidic, mixed and propagated[30,31]. On the other hand, performing the test "on" PPIs, provides useful information regarding the efficacy of acid-suppressive treatment and may detect a positive association between symptoms and weakly acidic reflux episodes - the large majority of episodes during acid suppressive drug -, which is a possible indication for anti-reflux surgery[32].

MANAGEMENT OF PATIENTS

Proton pump inhibitors

The large majority of patients with reflux symptoms receive PPI therapy once daily. If symptoms are not relieved, and after the presence of functional heartburn and CYP2C19 polymorphism have been excluded, several therapeutic strategies can be proposed. These include doubling the current PPI dosage or switching to another PPI.

Indeed, treatment failure may result from an insufficient dose of PPI. Doubling the PPI dose, giving PPI before breakfast and before dinner, is one of the most common therapeutic strategies adopted by practicing physicians having also been recommended in the 2008 American Gastroenterological Association guidelines for GERD, and confirmed by the Cochrane review[33,34]. However, is still not clear the dose-response relationship for heartburn resolution in either erosive esophagitis or non-erosive reflux disease patients[35]. Even if doubling the PPI dose has become one of the standard strategies, escalation of the PPI administration beyond the twice daily dosage, both for symptom control or for healing of erosive esophagitis, is not supported by strong clinical data. In the attempt to identify the patients who would benefit from dose escalation, Becker *et al*[36] performed pH-impedance monitoring in patients presenting persistent symptoms despite one month of standard PPI therapy. According to the pH-impedance data, two groups, one with and one without pathological findings, received high dose PPI (or fundoplication in a few cases). Imped-

ance was pathological in 40% of the non-responders, in whom escalating therapy was significantly more successful (90% relief) than in patients with normal findings.

Switching to another PPI is a very common, cost-effective, therapeutic strategy adopted in the management of patients who failed with the PPI once daily approach. In several studies, switching those patients who had failed with a PPI to esomeprazole, resulted in significant symptom improvement[37,38].

Antireflux surgery

Although it is well established that patients with symptoms not responding to PPIs have a less favorable post-operative clinical outcome compared to those patients responding to treatment, refractory GERD represents the most common (88%) indication for anti-reflux surgery. In a recent long-term follow-up study, 82% of the PPI-refractory patients reported that the preoperative reflux symptoms were completely resolved, and 94% were satisfied with the results of the surgery[39]. Several studies have suggested that a positive symptom-reflux association[40,41] and/or pathological AET[42,43], observed by impedance-pH monitoring in patients off PPI, predict a favorable response to surgery. It has been recently demonstrated that ranitidine 300 mg twice daily has a comparable efficacy respect to rabeprazole 20 mg twice daily when given on-demand for the treatment of NERD and both medications are associated with improvement of the quality of life[44].

It should be taken into consideration that the large majority of PPI-resistant patients do not present an erosive disease, therefore, given the possible adverse events associated with surgery and the recognized benign course of NERD, anti-reflux surgery should only be considered in selected patients, in whom objective evidence of reflux is revealed upon investigation. In summary, although surgery appears to be valid therapeutic option in GERD patients with typical symptoms who failed to respond to PPIs, further outcome and controlled studies, on a larger series of patients, using combined impedance-pH monitoring are warranted in order to draw definite conclusions.

Lifestyle modifications

It has been recently suggested that weight loss and elevation of head of the bed are effective in improving GERD symptoms in refractory patients, whilst no sufficient data support any other lifestyle modifications[45]. It has been recently reported that shorter dinner-to-bed time interval (less than 3 h) is significantly associated with persistence of GERD symptoms[46].

However, the relevance of lifestyle modifications in GERD patients who failed PPI treatment still remains to be fully elucidated.

Visceral pain modulators, psychological treatment

The therapeutic option represented by visceral pain modulators is highly attractive but, at present, studies specifically evaluating their efficacy in refractory GERD patients are still lacking. Tricyclic anti-depressants and selective serotonin reuptake inhibitors have been shown to relief esophageal pain in patients with non-cardiac chest pain[46-48]. Unfortunately, side effects of these drugs appear to be not uncommon and may hamper their usage.

It has been shown that refractory patients are more likely to have a psychosocial comorbidity[49], therefore it is conceivable that refractory GERD patients would benefit of psychological evaluation and treatment.

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