Prevalence and Clinical Characteristics of Refractoriness to Optimal Proton Pump Inhibitor Therapy in Non-erosive Reflux Disease

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Aliment Pharmacol Ther. 2018;48(10):1074-1081.

Abstract and Introduction

Abstract

Background: The real size of the gastro-oesophageal reflux disease (GERD) population not responding to proton pump inhibitor (PPI) therapy has still not been fully elucidated. Causes of PPI refractoriness include incorrect diagnosis and lack of adherence to therapy, in terms of incorrect dosage and timing.

Aims: To evaluate the prevalence of refractoriness to optimal PPI therapy and the contribution of non-erosive reflux disease (NERD), reflux hypersensitivity, and functional heartburn, to PPI refractoriness. The association of functional GI symptoms in non-responders was evaluated.

Methods: Frequency and severity of GERD symptoms (heartburn, regurgitation, chest pain), dysphagia, belching, epigastric pain, postprandial distress, irritable bowel syndrome (IBS), globus, and ear nose and throat (ENT) symptoms were evaluated in patients previously classified as non-responders. Patients with at least one of the oesophageal symptoms with a frequency ≥3/week were treated with esomeprazole 40 mg once daily for 8 weeks and then re-evaluated. Non-responders (patients with oesophageal symptoms ≥3 times per week) underwent 24 hour multichannel intraluminal impedance-pH monitoring.

Results: Of 573 consecutive patients, 92 with oesophageal symptoms and classified as PPI-refractory underwent the esomeprazole trial; 60 did not respond. IBS, epigastric pain, and post-prandial distress episodes were associated with a poor response on multivariate analysis. NERD, reflux hypersensitivity, and functional heartburn patients constituted 32%, 42%, and 26%, respectively of the PPI-refractory group.

Conclusions: True refractoriness in patients with GERD symptoms attending a secondary care setting is lower than previously reported. Following a careful history and optimal PPI dosing, the rate of refractoriness was 20%. True NERD constitutes only a third of the PPI-refractory group.

Introduction

Gastro-oesophageal reflux disease (GERD) is a common disorder affecting up to 20% of adults in Western countries.[1–3] Proton pump inhibitors (PPIs) represent the mainstay of treatment both for healing erosive oesophagitis and symptom relief. Although acid suppressive therapies have improved in efficacy over the last few decades, several studies have shown that a relevant proportion of patients with GERD symptoms (19%–44%) reports either partial or complete lack of response of symptoms to a standard PPI dose.[4–9] The management of refractory GERD patients is both a common and challenging task in routine clinical practice. Moreover, refractory GERD symptoms are associated not only with a significant decrease in all 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, medical consultations, and drug prescriptions.[10]

Various mechanisms involved in PPI refractoriness, in patients with GERD symptoms, have been proposed, such as peculiar patterns of reflux events, oesophageal hypersensitivity to physiological reflux (reflux hypersensitivity), mutations of cytochrome p450, and presence of functional heartburn, a condition which does not fall into the GERD spectrum.[11–16,8] It has been reported that beside the reflux pattern, assessed by 24–hour impedance-pH monitoring, the absence of oesophagitis, concomitant presence of functional disorders, and a body mass index (BMI) ≤25 are associated with PPI failure.[17]

In a proportion of non-responder GERD patients, the main cause of PPI refractoriness might be the lack of adherence to therapy, in terms of incorrect dosage and timing. Recently it has been shown that, in GERD patients, adherence to the prescribed PPI was achieved in only 55% of patients after 1 month, and 30% of patients 6 months after prescription. Moreover, the lowest levels of compliance were observed in non-erosive reflux disease (NERD) patients.[18] In a study focusing on patients with persistent GERD symptoms despite prolonged PPI treatment, the drug was appropriately administered in the fasting state, before breakfast, in less than 46% of them.[19]

To our knowledge, in most clinical studies focused on refractory GERD patients, either prospective or retrospective, adherence to PPI therapy was not checked and it might be, in part, involved in partial or nonresponse to PPIs. Moreover, several studies have evaluated patients with typical, oesophageal symptoms, more specific of GERD with those presenting with atypical and extra-oesophageal symptoms refractory to PPIs; few investigations were focused on selected groups of NERD patients with

oesophageal symptoms only.

Therefore, the real size of the GERD population not responding to an adequate PPI course has not been fully elucidated. Indeed, the largest series report a very high proportion of patients with symptoms refractory to PPIs, but with very different figures according to the various settings, much higher (up to 45%) in community-based and practitioner surveys, probably due to a less strict classification of patients and with several methodological limitations. Limitations in assessing the real PPI resistance include: (a) inconsistencies in the literature of the definitions used of partial and nonresponse, (b) the type of symptoms included in this definition, (c) the absence, in many studies, of baseline frequency and severity scores for heartburn and regurgitation, assessed by structured questionnaires, and (d) incorrect classification and inclusion of patients with functional heartburn, eosinophilic oesophagitis, and major motor oesophageal disorders.

The present study was therefore aimed at evaluating the real prevalence of refractoriness to an optimal PPI therapy in patients with oesophageal GERD symptoms and with a previous diagnosis of nonresponder, non-erosive, reflux disease. Moreover, the association of concomitant GI symptoms in patients with/without an optimal response was also evaluated. Finally, our study was aimed at evaluating the contribution of NERD, reflux hypersensitivity (RH), and functional heartburn (FH) to the refractory group.

Materials and Methods

Study Design

The NERONE (NERd Open study on real resistaNcE to PPI, EudraCT: 2011–005203–32) is a national, multicentre, prospective open study in consecutive patients with GERD symptoms attending the GI Units of Rome, Milan, Genoa, and Chieti University Hospitals. Inclusion criteria were age between 18 and 70 years, the presence of oesophageal symptoms (heartburn, regurgitation, noncardiac chest pain [NCCP]), and the absence of erosive oesophagitis and/or Barrett's oesophagus at an upper endoscopy performed within 2 years and following a 4–week pharmacological washout. According to the Montreal classification, we have distinguished patients with oesophageal syndrome (heartburn, regurgitation, and NCCP) from those with only extra-oesophageal symptoms or oesophageal injuries who were excluded from the final analysis.[20] A schematic representation of the study design is depicted in Figure 1. The study was approved by the Ethics Committee of the four University centres and written informed consent was obtained from all individuals.

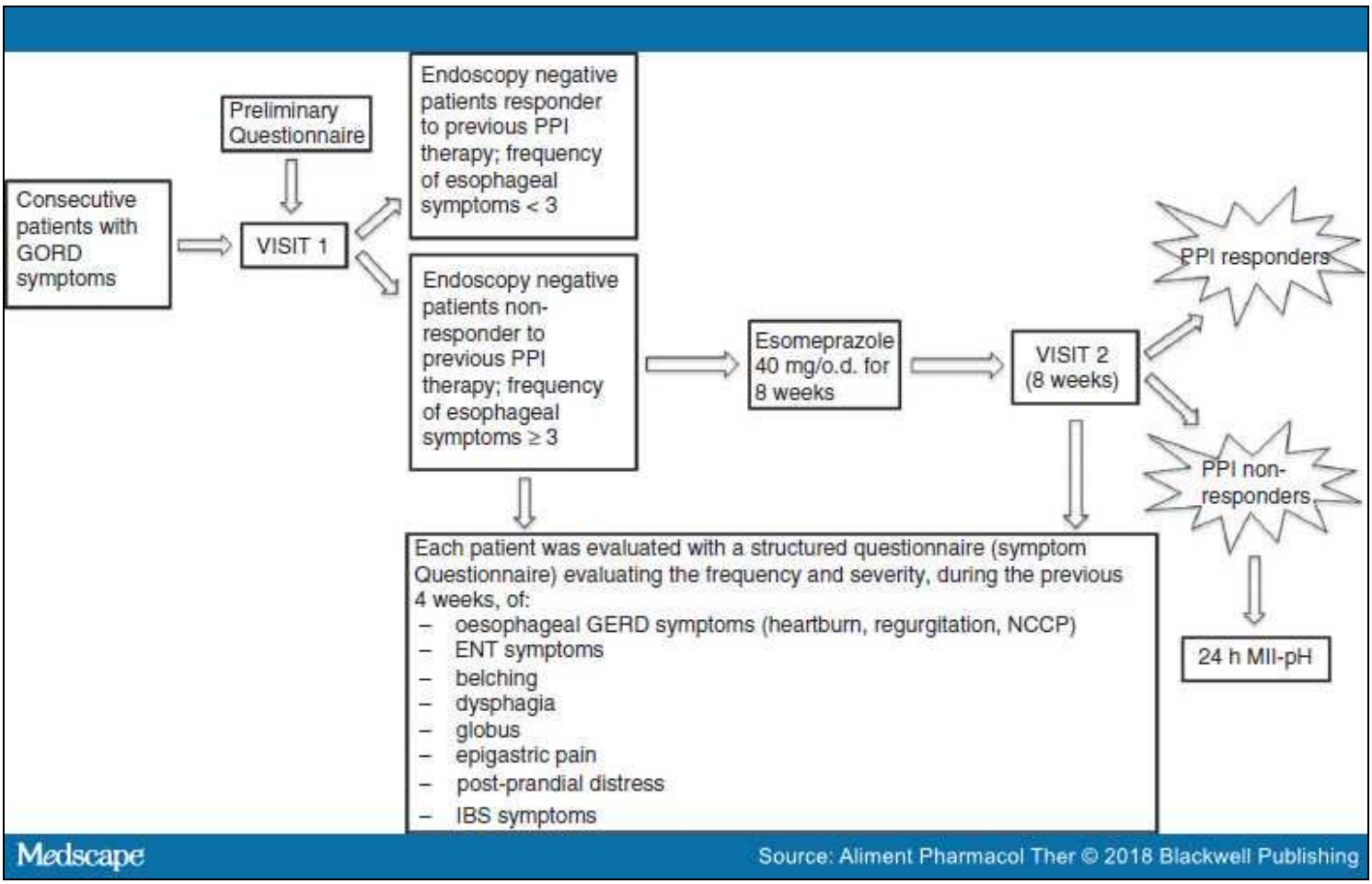

Figure 1.

Schematic representation of the study design. Patients were defined as nonresponders, at Visit 2, if oesophageal symptoms still occurred ≥3 times per week, following the 8–week esomeprazole treatment. PPI, proton pump inhibitor; MII-pH, multichannel intraluminal impedance-pH; IBS, irritable bowel syndrome; ENT, ear nose throat

Visit 1

During the first visit (Visit 1), all patients were evaluated with a preliminary questionnaire, assessing the demographic characteristics, presence of typical symptoms as well as of erosive oesophagitis and/or Barrett's oesophagus and the length, dosage, timing, and response to previous PPI courses. According to the preliminary questionnaire, only endoscopy negative patients presenting oesophageal symptoms with an unsatisfactory PPI response were eligible.

Following a proper pharmacological washout from PPIs and H2 antagonists, eligible patients filled out the Symptom Questionnaire, that is, a structured questionnaire including three items evaluating the frequency and severity, during the last 4 weeks, of the oesophageal symptoms (heartburn, regurgitation, and NCCP), and seven items assessing the frequency and severity of dysphagia, belch, epigastric pain, postprandial distress, irritable bowel syndrome (IBS), globus, and ear nose throat (ENT) symptoms (chronic cough, hoarseness, dysphonia). Frequency (number of episodes/week) and severity of each symptom were assessed with a 0–10 Likert scale. A composite score, defined as the mean of the frequency and severity Likert scale values, was also calculated in order to measure the impact of each symptom.

Both questionnaires were discussed with patients and filled out by the physicians. Subsequently, only those patients presenting at least one of the three oesophageal symptoms with a frequency ≥3 episodes/week were treated with esomeprazole 40 mg, once daily for 8 weeks. The principal investigators of each university centre provided the blisters of drug for each eligible patient.

Visit 2

Treated patients were re-evaluated with the same Symptom Questionnaire after 4 weeks (during a phone call) and 8 weeks (Visit 2), at the end of therapy, and the blisters of drug were returned in order to check the compliance (frequency and timing) at the end of PPI treatment. Patients were finally defined as non-responders, at Visit 2, if oesophageal symptoms still occurred ≥3 times per week, following the 8–week esomeprazole treatment.[21] Therefore, nonresponder patients underwent oesophageal manometry and 24 hours multichannel intraluminal impedance-pH (MII-pH), following at least 2–week of esomeprazole washout.

Oesophageal Physiologic Testing

To better define the localisation of the lower oesophageal sphincter (LOS), oesophageal manometry was performed prior to MII-pH monitoring with a water-perfused catheter incorporating three distal openings, radially orientated for LES pressure recording, and three side-hole recording sites at 5, 10, and 15 cm above the distal openings.

MII-pH was recorded with a 2.3 mm diameter polyvinyl assembly containing a series of electrodes, each 4 mm in axial length, spaced at 2 cm intervals (Sandhill Scientific Inc., Highlands Ranch, CO, USA). The signals from the impedance and pH channels were digitised at 50 Hz and stored in a separate data logger. Oesophageal pH was measured with an antimony pH electrode. The pH electrodes were calibrated using pH 4.0 and pH 7.0 buffer solutions before starting the recording. Patients were studied after an overnight fast of at least 10 hours. Following stationary manometry, the MII-pH assembly was passed through the nose, under topical anaesthesia, and positioned with the pH electrodes at 5 cm above the LES and at gastric level. In this position, impedance was measured at 3, 5, 7, 9, 15, and 17 cm proximal to the LES. Patients were asked not to lie down during the day, but only at their usual bedtime. Furthermore, patients were instructed to have three meals and two beverages at fixed times during the 24 hours measurement period. Event markers recorded occurrence of symptoms, meal times, and posture changes. Reflux events were detected and classified as liquid, mixed liquid-gas, and pure gas reflux episodes according to previously published criteria.[22] Acid exposure time (AET) was defined as pathological if the time at pH <4 exceeded 6% of the total recording time or if it was between 4% and 6% and number of reflux episodes was >80, according to recent Consensus of International experts.[23,24] The symptom association probability (SAP) for all reflux episodes was calculated according to the formula described elsewhere.[25] Heartburn, regurgitation, and chest pain were considered in the analysis of symptoms. Endoscopy negative patients with abnormal AET, irrespective of SAP, were defined as having NERD; patients with normal AET but positive SAP were reflux hypersensitivity (RH) patients; finally, patients with both normal AET and SAP were classified as functional heartburn (FH) patients according to Rome IV criteria for functional oesophageal disorders.[26]

Statistical Analysis

Age, sex, and BMI were presented as mean ± SD. Group means were compared using two-sample Student's *t* tests. The comparisons of groups were assessed by means of Fisher's exact tests. A composite score, defined as the mean of the frequency and severity Likert scale values, was calculated in order to measure the impact of each symptom. The risk of PPI refractoriness in the presence of dysphagia, ENT, belch, globus, IBS symptoms, epigastric pain, and postprandial distress was assessed using multivariable logistic regression models, adjusted for age, sex, and BMI. Results are reported as Odds Ratios (ORs) and 95% confidence intervals (CIs). Significance was achieved when the *P* value was <0.05. The statistical analysis was performed using STATA 14 for MAC.

Results

A total of 573 consecutive patients with symptoms attributed to GERD and poorly responder to a previous PPI course, attending the GI Units of Rome, Milan, Genoa, and Chieti University Hospitals were evaluated, during Visit 1, by means of the preliminary questionnaire and the symptom questionnaire. Among these, 481 patients (ie, 50 patients with previous evidence of erosive oesophagitis [20 grade A, 21 grade B, 9 grade C-D], 11 patients with Barrett's oesophagus, 205 patients whose oesophageal symptoms had responded to previous PPI therapy, 215 patients with predominant extra-oesophageal symptoms and with a frequency of the oesophageal symptoms <3 episodes/week) were excluded according to the study design. Therefore, only 92 patients, with a frequency of oesophageal symptoms of at least three episodes/week and without evidence of erosive oesophagitis at previous upper endoscopy, did not show a satisfactory symptom improvement to previous PPI treatments according to our structured questionnaires filled out in the presence of the physician. This group represents 31% of the whole cohort of 297 endoscopy negative patients referred to gastroenterologists for oesophageal GERD symptoms targeted as PPI refractory.

According to the study design, these 92 patients were treated with esomeprazole 40 mg o.i.d. for 8 weeks. Compliance to therapy, checked at phone call (4 weeks) and during Visit 2, was optimal in almost all patients. A total of 60 (37 female, mean age 47 years, range 23–68 years) out of 92 patients (65%) still reported a symptom frequency ≥3 times per week at Visit 2 and were, therefore, defined as nonresponders. The remaining 32 patients (18 female, mean age 51 years, range 25–66 years) (35%) resulted to be responders to the esomeprazole trial. No differences were found between responders and nonresponders in terms of sex and mean age. Mean BMI was not different between responders and nonresponders (22.6 vs 23.1, *P*: ns). hiatal hernia (>2 cm) was present in 9/60 (15%) nonresponders and in 4/32 (12.5%) responders to the esomeprazole trial (*P* = NS).

Symptoms Analysis in Responders and Nonresponders

Visit 1. During Visit 1, the 60 nonresponder patients presented a significantly higher prevalence of IBS symptoms, epigastric pain and postprandial distress episodes compared to responder patients. The prevalence of ENT symptoms, belch, globus, and dysphagia was comparable (). However, the mean composite scores of each symptom did not differ between responders and nonresponders ().

Table 1. Prevalence and clinical impact (composite score) of dysphagia, belching, epigastric pain, postprandial distress, irritable bowel syndrome (IBS), globus, and ear nose and throat (ENT) symptoms during visits 1 and 2

	Visit 1		Visit 2	
	Responders	**Non-responders**	**Responders**	**Non-responders**
Dysphagia	19% (1.7)	26% (1.3)	21% (1.2)	22% (1.3)
Belching	62% (6.2)	68% (7.2)	62% (5.2)	64% (5.4)
Epigastric pain	30% (4.9)	56%[a] (3.1)	30% (2.8)	40% (2.4)
Postprandial distress	46% (6.2)	79%[a] (3.2)	41% (4.8)	81%[a] (3.9)
IBS	26% (1.9)	50%[a] (1.9)	31% (1.8)	60%[a] (1.8)
Globus	38% (3.5)	41% (4.7)	39% (3)	41% (3.8)
ENT symptoms	79% (5)	69% (7.1)	80% (3.5)	60% (5.6)

[a] $P < 0.01$ vs responders.

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Results emerging from the multivariate analysis are summarised in . IBS symptoms, epigastric pain and postprandial distress episodes at Visit 1, were associated with a poor response to the esomeprazole trial.

Table 2. Risk of proton pump inhibitor refractoriness in the presence of dysphagia, ear nose and throat (ENT), belching, globus, irritable bowel syndrome (IBS) symptoms, epigastric pain, and postprandial distress

	OR (95% CI)	*P*
Dysphagia	1.1 (0.8–1.6)	0.5
Belching	1.1 (0.8–1.5)	0.6
Epigastric pain	1.5 (1.1–1.9)	0.02
Postprandial distress	1.7 (1.1–2.7)	0.002
IBS	1.4 (1.1–1.9)	0.02
Globus	1.1 (0.8–1.7)	0.4
ENT symptoms	0.9 (0.7–1.2)	0.5

Visit 2. During Visit 2, the 60 nonresponders to the esomeprazole trial still presented a significantly higher prevalence of IBS symptoms and postprandial distress episodes compared to responder patients. The prevalence of ENT symptoms, belch, globus, epigastric pain, and dysphagia episodes was comparable. In agreement with Visit 1 findings, the mean composite scores of each symptom did not differ between responders and nonresponders (). In both responder and nonresponder patients, prevalence and composite score of all symptoms did not significantly differ between Visit 1 and Visit 2, except for the composite score of epigastric pain, decreasing following therapy in the responder group.

Table 1. Prevalence and clinical impact (composite score) of dysphagia, belching, epigastric pain, postprandial distress, irritable bowel syndrome (IBS), globus, and ear nose and throat (ENT) symptoms during visits 1 and 2

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ENT symptoms	79% (5)	69% (7.1)	80% (3.5)	60% (5.6)

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Oesophageal Physiologic Testing

Among the 60 nonresponders patients who underwent conventional oesophageal manometry, four displayed evidence of ineffective oesophageal motility (IOM) and six presented motor abnormalities not fulfilling the criteria of specific motility disorder. No patients had evidence of achalasia and/or diffuse oesophageal spasm. The mean LOS resting pressure was 18.8 ± 7.1 mm Hg.

The 60 endoscopy negative patients not responding to the esomeprazole trial underwent 24 hours MII-pH monitoring, according to the study design. The mean number of reflux episodes was 64 ± 17 (range: 41–102). Patients displayed a mean number of 31 ± 11 acid reflux, 26 ± 11 mixed reflux, and 19 ± 11 proximal reflux episodes. Nineteen patients presented a positive AET (seven with positive SAP) (NERD patients) and 25 only a positive SAP (RH patients). Sixteen patients, having both negative AET and SAP, were finally classified as functional heartburn (FH) patients. IOM was observed in three NERD patients, one RH patient and in none of the FH patients. A schematic representation of the study population is depicted in Figure 2 The prevalence of each symptom, at Visit 1, was similar among NERD, RH, and FH patients and did not change significantly at Visit 2, although in NERD and RH patients, a trend for a reduction in epigastric pain was observed following the PPI course (). Figure 3 shows the prevalence of epigastric pain, postprandial distress, and IBS symptoms at Visit 2 in NERD, RH, and FH

patients compared with responder patients.

Table 3. Prevalence of dysphagia, belching, epigastric pain, postprandial distress, irritable bowel syndrome (IBS), globus, and ear nose and throat (ENT) symptoms, at visits 1 and 2, in non-erosive reflux disease (NERD), reflux hypersensitivity (RH), and functional heartburn (FH) patients

	NERD		RH		FH	
	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2
Dysphagia	31%	29%	22%	24%	18%	19%
Belching	71%	72%	88%	84%	51%	50%
Epigastric pain	55%	37%	54%	41%	48%	43%
Postprandial distress	74%	77%	81%	78%	82%	80%
IBS	55%	61%	52%	58%	48%	63%
Globus	42%	40%	38%	42%	43%	42%
ENT symptoms	66%	49%	62%	47%	81%	75%

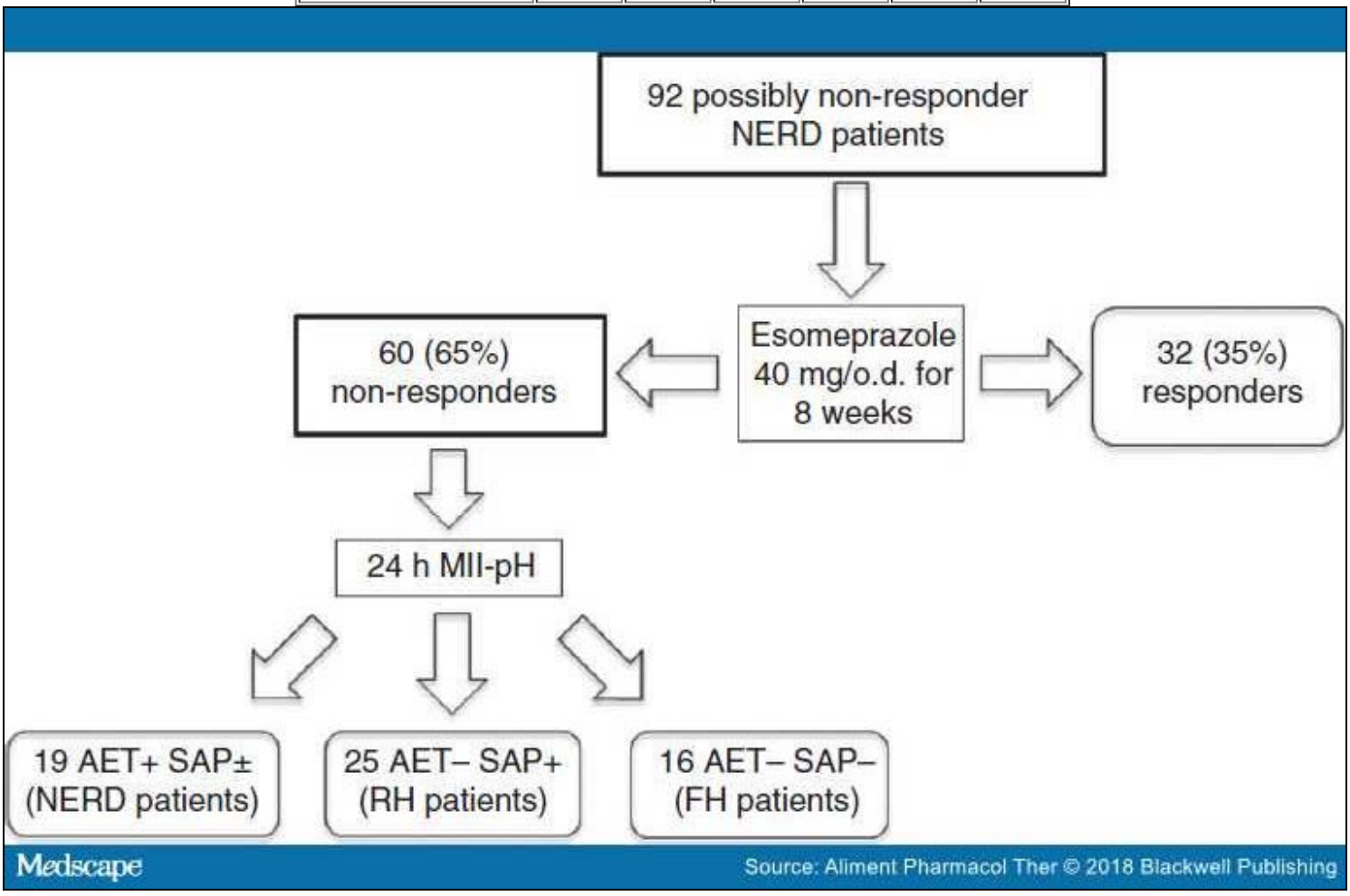

Figure 2.

Schematic representation of the refractory patients, according to the multichannel intraluminal impedance-pH (MII-pH) findings. AET, acid exposure time; SAP, symptom association probability; NERD, non-erosive reflux disease; RH, reflux hypersensitivity; FH, functional heartburn

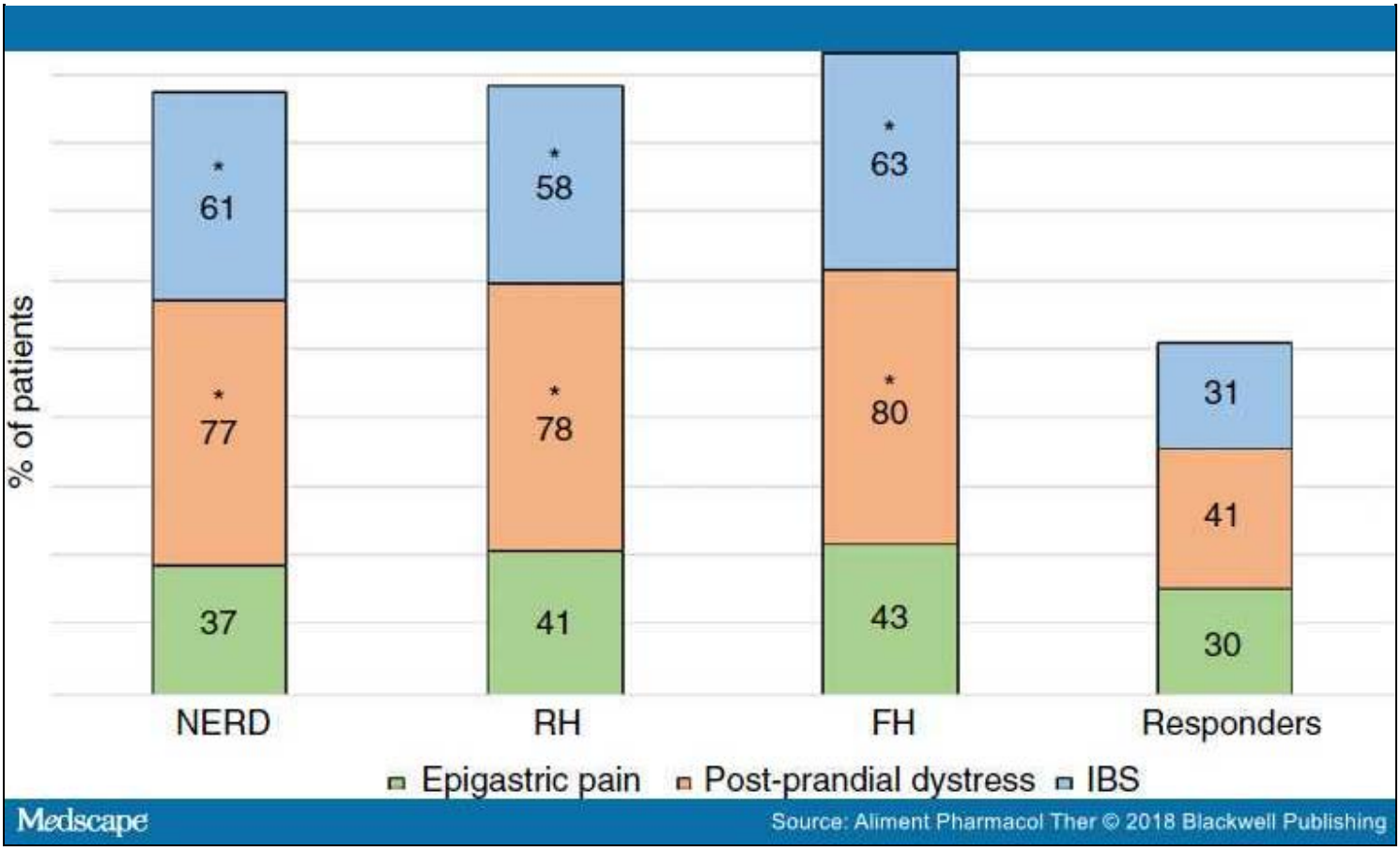

Figure 3.

Prevalence of epigastric pain, postprandial distress, and irritable bowel syndrome (IBS) symptoms, at Visit 2, in non-erosive reflux disease (NERD), reflux hypersensitivity (RH), and functional heartburn (FH) patients compared to proton pump inhibitor (PPI) responder group (*P < 0.05 vs responders)

Discussion

This is the first, prospective study evaluating the true refractoriness in patients with oesophageal reflux symptoms, and negative upper endoscopy, attending hospital GI Units for symptoms poorly responsive to PPI therapy and the contribution of NERD, reflux hypersensitivity, and functional heartburn to this group. We have decided not to include patients having only extra-oesophageal symptoms since (a) these symptoms alone have a very low sensitivity and specificity for GERD diagnosis, (b) these patients are quite heterogeneous, (c) the extra-oesophageal symptom pathogenesis is known to be multifactorial.[27–30] The first finding of our study is that among a large cohort of patients referred to gastroenterologists for oesophageal GERD symptoms previously defined as PPI refractory, only 31% (92/297) of them, when assessed with a structured questionnaire filled out at the presence of the physician, presented oesophageal symptoms not responding to a previous course of PPIs.

It has been previously suggested that the proportion of PPI refractory patients seen in a hospital out-patients clinic decreases considerably when an adequate PPI treatment is taken by the patient.[31] Our prospective study design allowed us to confirm these data by selecting true refractoriness among patients coming to our out-patients clinic with residual GERD symptoms.

Our data show that, when a PPI is taken continuously at adequate dose and for adequate length of time, refractoriness declines by one-third, "false" refractoriness being therefore 11% (32 out of 297 patients) of the whole cohort. Patients were taking various PPIs before entering our study whereas they underwent an 8–week course of esomeprazole during the study. Although few data are present in the literature, it is possible that switching to esomeprazole contributed to a better response at least in a subset of patients. It could be argued that a double dose of PPI was not used.[32,33] Indeed, our study was aimed at mirroring clinical practice where one single full dose is used in accordance with the regulations of the national health system in Italy and other European Countries. Furthermore, previous data have shown that refractoriness to a single dose of PPIs remains in most patients also when the dose is doubled.[34]

How does our prevalence of refractoriness compare with previous reports? In the present study, true refractoriness of oesophageal symptoms was present in 20% of the whole cohort (60 of 297 patients), a lower proportion than in most of previous reports. Studies looking at "raw refractoriness" (ie, without performing a proper PPI trial) have shown proportions of 17–45% in primary care and of 30% in secondary care.[33,34] Definition of refractoriness has been different in the various

studies. We have chosen a definition of residual oesophageal symptoms, occurring ≥3 times per week, which is currently widely used.[21] In agreement with previous studies, the presence of gut-brain axis disorders (irritable bowel syndrome, dyspepsia, postprandial distress) was a risk factor for refractoriness.[17] It is of interest that this association was seen only when occurrence of GI symptoms was considered (significantly more patients were affected by functional GI symptoms in the refractory group); however, the impact (composite score) of these functional GI symptoms was comparable between patients responders and nonresponders to the esomeprazole trial suggesting that, when present, they carried the same burden in both groups. The presence of globus, dysphagia, and ear nose throat symptoms was irrelevant for being or not refractory to PPIs. It is interesting to note that the frequency of epigastric pain in NERD and reflux hypersensitivity refractory patients decreased after esomeprazole (Visit 2) becoming similar to responders, suggesting that the epigastric pain is an acid-related symptom, at least partly responding to PPIs.

Performing MII-pH off PPI in our refractory patients has allowed to evaluate, according to the recent classifications, the proportion of patients who were really troubled by GERD (increased reflux and/or positive symptom/reflux association) from those who had functional heartburn.[23,35] In agreement with a study done in a similar cohort of PPI refractory patients, functional heartburn was diagnosed in up to one-third of patients.[36] Recently, Roman et al have performed MII-pH monitoring in 78 PPI refractory patients and their results showed a slightly higher percentage of functional heartburn (55%).[36] However, it has to be noted that in the above-mentioned study, also patients in whom ambulatory 24 h impedance-pH was performed for PPI refractory extra-oesophageal symptoms were included.

Another interesting finding, in our series, is that the association between true refractoriness and gut-brain axis disorders was independent of the diagnosis of NERD, reflux hypersensitivity, or functional heartburn. A previous study looking at the whole population of NERD and functional heartburn, that is, without data on treatment outcome, had shown that functional heartburn patients had higher prevalence of IBS and dyspeptic symptoms.[37] However, it has been previously observed that, in a population of patients with reflux symptoms, functional dyspepsia and IBS symptoms predicted refractoriness also in the subset of patients with GERD, as diagnosed by ambulatory 24 hours impedance-pH monitoring.[17] These findings provide further support to the hypotheses that refractory reflux symptoms, functional dyspepsia, and IBS share the same underlying mechanisms (ie, an increased visceral perception).[38] It would be interesting to know whether the results of the MII-pH monitoring are able to improve the management of true refractory patients. Is increase in antisecretory medications useful in NERD and use of pain modulators in reflux hypersensitivity and functional heartburn? Or will all three groups benefit from pain modulators (administered together with PPIs in NERD patients)? These outcome data were not part of our study and will be, hopefully, subject of further research.

Strength of our study are the prospective and multicentre design allowing a considerable number of patients to be evaluated, use of a structured questionnaire, measurement of compliance to PPIs and a distinction of true NERD, reflux hypersensitivity, and functional heartburn patients, by means of MII-pH monitoring, within the PPI refractory group. Moreover, the risk of PPI refractoriness in the presence of dysphagia, ENT, belch, globus, IBS symptoms, epigastric pain, and postprandial distress was explored using a model of multivariable analysis that removes the effect of main potential confounders, that is, age, gender, and BMI. A limitation of our study is that it was performed in secondary care centres and caution should be exerted to generalise results to the primary care setting, although data in the literature suggest that refractoriness should not be higher. Moreover, we have included only patients with oesophageal symptoms poorly responder to PPIs in order to have a more homogeneous group of GERD patients and results in patients mainly referred for extra-oesophageal symptoms could be different.

In conclusion, our study has shown that true refractoriness to PPIs in patients with oesophageal GERD symptoms and a negative upper GI endoscopy attending a secondary care setting is lower than previously reported and that true NERD contributes only by one-third to the PPI refractory group.

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Acknowledgement
We wish to acknowledge Astra Zeneca Italy for providing the time-scheduled blisters and drug for this study.

Declaration of personal and funding interests
None.

Authorship

Guarantor of the article
Mentore Ribolsi.

Aliment Pharmacol Ther. 2018;48(10):1074-1081.