Gastro-esophageal reflux disease: new therapeutic aspects

Symposium held in Bologna on March 27, 2015, during the 21st National Congress of Digestive Diseases
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Introduction

For many years, gastro-esophageal reflux disease (GERD) was considered to be strictly correlated with the presence of acid reflux, and acid secretory inhibitors were the mainstay of therapy. In recent years, however, several publications and systematic reviews have highlighted that 20-40% of patients with GERD do not respond (either completely or partially) to proton pump inhibitors (PPIs), thus showing that acid is often not the only pathogenetic factor involved. It is now clear from the medical literature that the majority of patients with GERD have non-erosive disease, meaning the absence of macroscopic alterations of esophageal mucosa. However, biopsy and histological examination have demonstrated the presence of microscopic esophagitis, which is primarily (but not only) characterised by altered dilation of intercellular spaces, which is typical of GERD. In evaluating patients with GERD (especially those who show no benefits from PPIs), it is important to define the type of gastro-esophageal reflux (acid, weak acid, non-acid, liquid, or gaseous) and to identify the presence of microscopic lesions in endoscopically normal mucosa. The therapeutic approach in these ‘difficult’ patients is based on products that act on different pathophysiological mechanisms, including those that involve the protection of the esophageal mucosa, a therapeutic target that has been largely overlooked.

Medical therapy with GERD: the role of PPIs

The role of PPIs in the management of GERD is two-fold, namely diagnostic and therapeutic. Presently, in GERD with typical symptoms, an initial treatment with PPIs is of relevance in confirming the “clinical” diagnosis, with good sensitivity and specificity. In management of GERD, PPIs represent the mainstay of medical therapy, just as they are the first-choice in other acid-related pathologies. In the 1990s, it was demonstrated that the frequency of symptoms in GERD is directly correlated with exposure to acid of the distal esophagus. Two classes of drugs, aimed to reduce the acid secretion at the gastric level, are nowadays available: H2 receptor antagonists and PPIs. Both classes of drugs are thereby able to reduce the exposure of the esophageal mucosa to acid. H2 antagonists have a more rapid onset of action than PPIs, which, however, have a longer duration of action. PPIs are effective in the resolution of symptoms and the healing of esophageal injuries, and when administered at high or low doses, help maintain patients in long-term remission. A recent Cochrane review demonstrated that this class of drugs is more effective in resolving the typical symptoms of GERD than either H2 antagonists or prokinetics (Table I). It is nonetheless important to underline that PPIs reduce the exposure of esophageal mucosa to acid and modify the composition of the reflux, but do not reduce the total number of gastro-esophageal reflux events. Moreover, their efficacy on belching reduction is clearly inferior to that on heartburn resolution, with a therapeutic gain that is less than 50%.

By endoscopy, patients with typical symptoms of GERD may show erosive esophagitis (with or without complications, stenosis, or Barrett’s esophagus) or normal mucosa, which is seen more frequently (about 65% of cases). Patients with this latter phenotype are referred to as being affected with non-erosive reflux disease (NERD). Several systematic reviews and meta-analyses have documented that the clinical efficacy of PPIs is generally less than 50% in patients with NERD. The reason of this low efficacy is related to the complexity in the definition of NERD patients which can be classified in at least four subgroups with negative endoscopy and reflux symptoms. Studies using pH impedance test have allowed for identification of the following populations:

- patients with NERD;
- patients with an esophagus that is hypersensitive to acid;
- patients with an esophagus that is hypersensitive to non-acid;
- patients with functional heartburn.

Obviously, the first two groups of patients (in which acid has a predominant pathogenetic role) adequately respond to PPIs, while there is practically no clinical efficacy in the other two groups. As addi-
tional confirmation of the importance of correct patient selection \(^2\), a recent meta-analysis \(^3\) demonstrated that when a diagnosis of NERD is made with negative endoscopy and positive pH measurements, the response of patients to PPIs is similar to that in erosive disease. There is also a subgroup of patients affected by esophageal hypersensitivity to acid in whom normal exposure of the esophageal mucosa to acid, with a pH value within normal limits is observed. Typical symptoms can be associated with either non-acid gastro-esophageal reflux (in this case therapy with PPIs is not effective \(^1\)) or acid gastro-esophageal reflux associated with visceral hypersensitivity (Fig. 1) \(^4\).

Patients with functional heartburn, included in the Rome III classification among functional gastrointestinal disturbances \(^5\), present a pH impedance profile that is normal, show no correlation between symptoms and ‘physiological’ reflux episodes and demonstrate visceral hypersensitivity \(^6\). This group of patients often has symptoms consisting of nausea, borborygms, heartburn and early satiety, which reflect a functional disorder of the digestive system \(^7\). In patients with non-erosive disease who do not respond to therapy with PPIs, functional investigations with pH impedance are useful. The presence of ‘residual’ acid reflux during treatment necessitates a dose increase \(^8\), which is usually able to control symptoms. In the presence of weak acid or non-acid reflux, just as for patients with functional heartburn, therapeutic alternatives to PPI should be taken into consideration (Fig. 2).

Patients with GERD may refer extra-esophageal symptoms in the presence or absence of typical symptoms. The Montreal classification \(^9\) describes some of the associated symptoms (chronic cough, chronic laryngitis, asthma reflux and dental erosion) that have been definitely established, and others that have been proposed (pharyngitis, sinusits, chronic otitis and idiopathic pulmonary fibrosis). For some of the conditions, therapy with PPIs can be effective when administered at high doses (double dose) for at least 2-3 months. Improvement of extra-digestive symptoms (e.g. asthma) is, in fact, very slow. It is nonetheless important to underline that the majority of studies in this area have examined small numbers of patients with experimental designs that were not methodologically correct and with results that were often discrepant.

In conclusion, PPIs still represent first-choice medical therapy of GERD. However, it should be kept in mind that their clinical efficacy is different in different patients’ population \(^10\): the efficacy of PPIs is much greater in erosive disease and progressively decreases in various subgroups of NERD or in the presence of extra-esophageal symptoms (Fig. 3).

### Medical therapy of GERD: beyond PPIs

#### Introduction

Recent findings have confirmed that GERD has a multifactorial pathogenesis that mainly implies a disorder of gastric and esophageal motility (with malfunctioning of the inferior esophageal sphincter), which is accompanied by reduced salivary secretion and altered defence mechanisms of the esophageal mucosa. Secretion of gastric acid is, in the majority of cases, within normal limits \(^11\). In spite of this, antise-
cretory drugs (and PPIs in particular) are widely utilised for medical therapy of GERD and can be considered as the first therapeutic choice with the aim of reducing the lesions caused by acid gastric reflux in the esophagus. The clinical efficacy of PPIs and the availability of intraluminal pH measurements in past years primarily focused attention on the acid component of the reflux. As a consequence, gastro-esophageal reflux and acid reflux have become synonymous. However, aberrant sphincter function allows not only acid to reflux in the esophagus, but the entire gastric content including food and bile with variable pH. Studies with pH impedance have clearly demonstrated that the reflux can be acid, weakly acid, or non-acid, as well as gaseous or mixed, both before and during therapy. PPIs, which decrease both volume and concentration of gastric juice, can reduce the exposure of the distal esophagus to acid, but do not influence other types of reflux. Considering this, there is thus the need for additional drugs that can act on GERD through mechanisms that are different from inhibition of acid secretion. Moreover, PPIs have an effect on reflux disease that is only palliative as they do not act on the underlying physiological alterations. Both literature data and clinical experience suggest that at least 20% of patients with GERD do not respond adequately to therapy with PPIs. The clinical efficacy of PPIs, compared to that observed in patients with esophageal lesions, is lower in NERD. The main reason for this is due to the fact that NERD is a heterogeneous group that can be divided into several subgroups; in some of these subgroups, acid reflux does not play a pathogenetic role. In such patients, there is almost no response to PPIs. The response to PPIs is often suboptimal even in patients with atypical symptoms and extra-esophageal manifestations of GERD and in those with functional heartburn (Table II).

**Management of patients with partial response to PPIs**

Management of patients with symptoms (typical or atypical, which do not adequately respond to PPIs) requires a gradual approach, initially based on the use of add-on treatments in addition to antisecretory therapy. In the case of failure, an esophago-gastro-duodenoscopy with biopsy should be performed (even on macroscopically normal esophageal mucosa), together with functional exploration using 24-hour pH impedance (Fig. 4). Esophageal manometry and dynamic radiological exam of the esophagus are needed only in the presence of dysphagia or thoracic non-cardiac pain or in planning antireflux surgical intervention.

**What drugs in addition to PPIs?**

The available pharmacological options include systemic and topical therapies.
Systemic drugs
Gastro-esophageal reflux inhibitors
The main systemic drugs, currently defined as gastro-esophageal reflux inhibitors, are able to reduce the number of inappropriate releases of the lower esophageal sphincter (LES), which is the most important pathogenic mechanism responsible for GERD 29. Experimental studies have demonstrated that different classes of drugs (anticholinergics, CCK1 receptor antagonists, NO synthase inhibitors, opioid receptor agonists, CB1 receptor antagonists, GABAB receptor agonists and antagonists of metabotropic glutamate receptors, Mglu5) are also able to inhibit transitory releases of the LES. However, only some molecules of the latter two classes are presently in different phases of clinical investigation 21 29. The only gastro-esophageal reflux inhibitor currently available is baclofen, which is an antispastic GABAB agonist. Even if baclofen can decrease reflux and improve the clinical situation, its use is limited by the need for a high number of daily doses and by adverse effects (insomnia, nausea, vertigo, muscle weakness, etc.) 30 31. The development of similar drugs with a better tolerability profile has been discontinued due to the low efficacy observed 32.

Prokinetic drugs
GERD is mainly a disorder of gastro-esophageal motility 27. Several pathophysiological
studies have shown that gastric emptying is delayed in 30-40% of patients with GERD.

In patients with gastric motility disorders, the exposure of the distal esophagus to acid is increased by the greater availability of the gastric content that is accessible for reflux. Prokinetic drugs are thus a rational approach to management of GERD either as monotherapy or in combination with antisecretory agents. Following marketing withdrawal of cisapride due to its cardiotoxicity, no prokinetic drugs are currently available that have documented clinical efficacy in GERD. Metoclopramide and domperidone, still used in general medicine, have limited efficacy and are associated with significant adverse events, including both neurological (tardive dyskinesia) and cardiovascular events (ventricular arrhythmia and sudden death), respectively.

**Antidepressants**

Hypersensitivity of the proximal esophagus is related to peripheral sensitivity and/or esophageal mechanoreceptors either directly (through components of the gastric reflux content in the lumen) or indirectly (mediated by pro-inflammatory molecules whose expression is increased in the presence of macro- or microscopic esophagitis). The contribution of visceral hypersensitivity (already reported in erosive disease) to the symptoms of GERD increases in NERD form and becomes predominant in functional heartburn. NERD, which is the most prevalent form of GERD in clinical practice (60-70% of patients), can be considered as an acid-related disease that often overlaps with visceral sensitivity disorders. The use of antidepressants (SSRIs – selective serotonin reuptake inhibitors – and tricyclics) is justified by their ability to modulate esophageal sensitivity, which is often altered in patients.
with GERD. Antidepressants can also act on gastrointestinal secretions and motility. In particular, a meta-analysis showed as SSRIs, in contrast to tricyclic agents, are effective in refractory disease. Their use, however, is limited by adverse effects that are associated with high rates of treatment discontinuation, which was reported to be 31% in a recent meta-analysis.

Topical agents
Alginate-containing formulation
A large number of studies documented the ability of formulations containing alginate combined with antacids to generate a mechanical barrier against reflux at the level of the cardias. It should be underlined, however, that most of these studies were performed with Gaviscon, and that given the different compositions of commercial formulations it is not possible to extend these results to other formulations. Scintigraphic studies and magnetic resonance with three-dimensional image reconstruction has shown how the alginate raft, floating on the gastric content, is localised at the level of the gastro-esophageal junction below the gaseous bubble. The ability to reduce the proximal extension of the reflux and exposure of the esophagus to acid, confirmed by 24-hour pH impedance studies, is useful in supra-esophageal manifestations of GERD where the inhibitory activity of alginate on peptic activity is also important. A phenomenon that explains the high efficacy of these preparations and that also clarifies why reflux symptoms are particularly prominent following a meal, when the gastric pH is highest due to the buffering effect of food, invokes the so-called post-prandial ‘acid pocket’, or the collection of not buffered acid juice that floats above swallowed food. Considering its localisation at the level of the gastro-esophageal junction, the alginate raft can neutralise the content of the acid pocket or move it away from the gastro-esophageal junction, as documented in a clinical study. For these reasons, the addition of alginate-containing formulations to PPIs provides significant benefit in patients with both typical and atypical symptoms.

ESOXX® ONE
Gastro-esophageal reflux is present in all individuals, especially after an abundant meal rich in fats. Indeed, this is a physiological phenomenon, generally asymptomatic, which due to efficient clearance and defence mechanisms of the esophageal mucosa does not cause mucosal damage. The integrity of the esophageal mucosa depends on a delicate equilibrium between aggressive factors (acid, pepsin, biliary and pancreatic secretions) and protective mechanisms (e.g. salivary secretions, secretion of mucus and bicarbonates and the impermeable nature of the mucosa).

The resistance of the esophageal mucosa does not depend on any single factor, but rather on several structures and the function of the mucosa that interact in a synergic manner to create an integrated system of defence. Protective mechanisms are generally grouped in three distinct categories: pre-epithelial (salivary secretion, secretion of mucus and bicarbonates), epithelial (cells layering the squamous epithelium that limit the retro-diffusion of H+ ions favouring their neutralisation) and post-epithelial (primarily mucosal blood flow that provides additional bicarbonate for neutralisation in addition to oxygen and nutrients, favouring cellular repair mechanisms). Some studies have demonstrated that pre-epithelial defence mechanisms are defective in patients with GERD: both salivary secretion and frequent swallowing are significantly reduced, which leads to a decrease in esophageal clearance. Dilation of intercellular spaces, which is correlated to transepithelial resistance, and the reduced basal impedance of the esophageal mucosa in patients with reflux disease (erosive and non-erosive), reflects a reduction in epithelial defence mechanisms. Despite evidence for reduced mucosal integrity, stimulation of defence mecha-

**Figure 5.** Integrity of esophageal mucosa: an equilibrium between aggressive factors and protective mechanisms.
nisms and/or protection of the mucosa, with the exception of the initial attempts with sucralfate\textsuperscript{46}, have been only rarely considered as a therapeutic target in the treatment of GERD\textsuperscript{47}. The recent availability of ESOXX\textsuperscript{®} ONE, specifically developed to protect esophageal mucosa, has provided a novel therapeutic approach, which is undoubtedly more appealing from a pathophysiological standpoint than inhibition of acid secretion.

ESOXX\textsuperscript{®} ONE, a product developed for protection of the esophageal mucosa, contains two naturally-occurring compounds, hyaluronic acid (HA) and chondroitin sulphate (CS) distributed in a highly bio-adhesive carrier, poloxamer 407\textsuperscript{48}, which ensures an extended contact time with the esophageal mucosa following oral ingestion:

- **HA** has an important role in processes that involve the extracellular matrix (repair of lesions, regeneration, morphogenesis), thus favouring healing of mucosal lesions (even microscopic)\textsuperscript{49};

- **CS** has a protective effect on the mucosa, reducing the damage induced by acid and pepsin present in the gastric content that refluxes in the esophagus\textsuperscript{50};

- **Poloxamer 407** binds to both components to generate a macromolecular complex that forms physical barrier against various types of harmful agents (liquid or solid) and fluids (acids, weak acids, alkaline).

The “barrier” effect of ESOXX\textsuperscript{®} ONE has been ex vivo studied in a pig esophagus model perfused with hydrochloric acid solutions (with and without pepsin)\textsuperscript{51}. The mucosal damage, evaluated by histology, is followed by an increase in permeability, which is observable by an Evans Blue staining of the mucosa that is directly proportional to the damage extension. Pre-treatment with ESOXX\textsuperscript{®} ONE completely prevents the alterations in mucosal permeability induced by both types of harmful agents (Fig. 6). The protective effects of ESOXX\textsuperscript{®} ONE persisted even after washing the esophageal mucosa before acid-peptic perfusion, thus confirming its elevated adhesion to complex macromolecules and the long-lasting persistence of the barrier effect\textsuperscript{52}.

In a pilot study\textsuperscript{52} with a cohort of unselected patients with acid-related symptoms (heartburn, belching, epigastric pain and dyspepsia), ESOXX\textsuperscript{®} ONE administration was shown to be significantly more effective and faster than placebo in improvement of global symptom scores. A randomised, double-blind, placebo-controlled trial was later carried out in patients with NERD in which ESOXX\textsuperscript{®} ONE was administered in crossover with placebo for 2 weeks\textsuperscript{53}. Significant improvement was observed on global symptoms, heartburn and belching (Fig. 7). This latter finding is particularly interesting considering the limited efficacy of PPIs on belching in GERD, which is very difficult to control\textsuperscript{5}. This data thus support the use of ESOXX\textsuperscript{®} ONE in GERD that was refractory to PPIs, which is unfortunately common in clinical practice\textsuperscript{27}.

The results of this double-blind, placebo-controlled, multicentre study demonstrated that ESOXX\textsuperscript{®} ONE was more significantly effective in the resolution of symptoms than placebo, with a consequent improvement in the quality of life (Table III). In all these studies, the safety profile of ESOXX\textsuperscript{®} ONE was similar to placebo, as expected with a product with no systemic absorption.

**Conclusions**

Even if the protective mechanisms of the esophageal mucosa have been identified and studied in detail, they have rarely been considered as therapeutic targets in clinical practice. The recent availability of

**Figure 6.**
Permeability of porcine esophageal mucosa after perfusion with Evans Blue and different solutions (from Di Simone et al., 2012, mod.)\textsuperscript{51}.
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ESOxx® ONE represents an effective support to PPIs therapy and a welcome addition to the therapeutic armamentarium for GERD: the use of ESOxx® ONE in addition to PPIs is undoubtedly useful to improve therapeutic response in cases of treatment failure or inadequate response. Although not yet observed in the current clinical experience it is plausible that the long-term administration of ESOxx® ONE can extend remission of disease and delay inevitable recurrences, thereby modifying the natural history of the GERD disease.

Figure 7. Efficacy of ESOxx® ONE on resolution of symptoms in patients with NERD: randomised double-blind trial (from Palmieri et al., 2013, mod.)

Table III. Efficacy of ESOxx® ONE in association with PPIs in resolving symptoms in patients with GERD who are refractory to acid secretion inhibitors alone (from Savarino et al., in press). Multicentre, randomised, double-blind, placebo-controlled study.

<table>
<thead>
<tr>
<th>Study endpoint</th>
<th>ESOxx® ONE</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with reduction in TSS by at least 3 points</td>
<td>52.6%</td>
<td>32.1%</td>
<td>0.01</td>
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<tr>
<td>No. of patients with 50% reduction in TSS</td>
<td>38.2%</td>
<td>23.1%</td>
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<td>No. of patients with reduction in TSS at last control</td>
<td>78.9%</td>
<td>56.4%</td>
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<td>Change (±SD) in TSS after treatment</td>
<td>-3.1 ± 3.1</td>
<td>-1.5 ± 3.0</td>
<td>0.002</td>
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</tbody>
</table>

After treatment with ESOxx® ONE significant improvement was observed in the quality of life (evaluated with SF-36 questionnaire).

TSS: total symptom score (heartburn, retrosternal pain, belching, acid taste in mouth)

References
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