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Pharmacologic treatment of GERD in adolescents: Is esophageal mucosal protection an option?

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Abstract

Background: Gastroesophageal reflux disease (GERD) is still a challenging and difficult to treat condition in children. Although acid suppression represents the mainstay of treatment in adolescents, it is not devoid of adverse events, especially in the long-term.

Objectives: In this investigation we explored a new therapeutic avenue in GERD, that is esophageal mucosal protection.

Design: To this end, we performed an investigator-initiated, retrospective study to evaluate the efficacy and safety of a short-term treatment with Esoxx™ medical device in 25 adolescents with GERD-related symptoms. This mucoadhesive formulation contains two natural mucopolysaccharides (sodium hyaluronate and chondroitin sulphate) and adheres to the esophageal mucosa, exerting a protective effect against refluxed gastric contents and allowing mucosal healing.

Methods: Heartburn, epigastric burning and post-prandial regurgitation were scored with a pain VAS scale and re-evaluated after 3-week treatment with Esoxx (one stick post-prandially, three times daily).

Results: All patients completed the treatment without adverse effects and with good tolerability and compliance. All the three major symptoms significantly ($p<0.001$) improved after treatment. No patient required additional investigation (i.e. upper Gastrointestinal endoscopy) or medication (i.e. antisecretory drugs).

Conclusion: The results of this pilot study suggest that esophageal mucosal protection is a promising therapeutic avenue for GERD also in children. Provided, these data be confirmed by a large, randomized clinical trial, this medical device can enter our therapeutic armamentarium against this challenging disease.

Keywords: children, Esoxx™, GERD, mucosal protection, treatment

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Introduction

Gastroesophageal reflux (GER) is the passage of stomach contents into the esophagus. It is a normal physiologic process in both adults and children. It occurs throughout the day in infants and less often in children and adolescents, typically after meals. It may be asymptomatic or cause mild, non-troubling symptoms such as regurgitation or occasional vomiting. However, when reflux of gastric contents causes troublesome symptoms and/or complications, it represents a pathological condition named gastroesophageal reflux disease (GERD).[1]

Symptoms suggestive of GER are not rare in childhood and are a major reason for parental concern irrespective of the child's age.[2] Epidemiologic studies are complicated by unreliable reporting of symptoms in younger children (<8 years) and infants, in whom often are the parents who interpret symptoms as being troublesome or not. Therefore, the prevalence of GERD is influenced by the subjective interpretation of the child, the parents and the health-care professionals, since not all patients with GERD develop *objective* symptoms and signs such as esophagitis. It is estimated that in older children and

adolescents, the overall prevalence of GERD in Europe ranges from 10 to 20%,[1] with a lower proportion of patients needing some investigation or pharmacologic intervention. As a rule, a comprehensive history and clinical examination are sufficient in most infants and children to diagnose GERD, but judicious investigations are necessary in some patients.[3,4] Although endoscopy with biopsy and histologic evaluation represents the gold standard for detection of mucosal lesions,[5,6] the prevalence of erosive esophagitis in children is lower compared with adults,[7,8] with up to 80% of them belonging to one of the three NERD phenotypes.[9]

Like in adults,[10] GERD is primarily a motor disorder and its pathogenesis is multifactorial.[11] The main motility abnormalities include an impaired function of the lower esophageal sphincter (LES), an abnormal esophageal clearance, and a delayed gastric emptying in up to 40% of cases. The presence of hiatal hernia favors reflux, but this association is not mandatory. The ultimate consequence of the above motor abnormalities is the presence of acid in the wrong site (i.e., in contact with the esophageal mucosa).[10,11] In addition, the amount of reflux increases markedly after meals in both healthy subjects and GERD patients, an event almost exclusively due to the increase of transient (inappropriate) LES relaxations by meal-induced gastric accommodation.[12] Even though the pathophysiology and symptoms of pediatric GERD (especially older patients) are similar to those in adults, children may also present with a wide range of distinct gastroesophageal and extra-esophageal symptoms and potential complications.[2]

Treatment of GERD in adolescents usually starts with lifestyle changes, although their effectiveness has not been clearly shown like it was in infants and children[4] as well as in adults.[13] If drug therapy is deemed necessary, the treatment can rely on acid-lowering drugs and prokinetic agents.[5] Since high-quality evidence regarding the surgical management of GERD in the pediatric population is lacking,[14] anti-reflux surgery should be reserved to selected patients, that is, those with symptoms refractory to medical therapy or with GERD-related life-threatening complications.[3]

Conversely from adult patients, gastric acid secretion in children with GERD has not been extensively studied. However, some investigations found that patients with severe disease[15] or those needing surgical therapy[16] display acid hypersecretion. These findings provide a rationale for the use of acid-lowering drugs in the treatment of GERD in children. Indeed, antacids will neutralize intragastric acid while H_2-receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) decrease acid secretion, all reducing the aggressiveness of the gastric content refluxed into the esophagus. Poorly absorbed antacids (like magnesium hydroxide and/or aluminum hydroxide as well as calcium carbonate) in large amounts are as effective as an H_2RAs in medical treatment GERD in children.[17] However, their administration has been followed by plasma aluminum levels previously associated with toxicity in patients with renal failure after chronic exposure to this metal.[18] Because of this concern and because of their short duration of action, antisecretory drugs have represented the mainstay of the medical treatment of GERD. Their clinical efficacy has been shown in many studies,[19,20] with PPIs often preferred over H_2RAs because of their intrinsic pharmacologic properties.[3] The greater pharmacodynamic effect of PPIs depends on their ability to block the final step in the production of acid, regardless the secretory stimulus. Moreover, PPIs are relatively more effective during the daytime than the nighttime and this leads to a better control of postprandial reflux events.[21] However, conversely from adult GERD,[22] the superiority of H_2RAs over PPIs has not yet definitely demonstrated in children.[23] In addition, all H_2-blockers but famotidine have recently been withdrawn from the market because of nitrosamine impurity[24] and therefore not prescribed anymore.

Although PPIs represent one of the safest drug classes available and have been used worldwide for more than 30 years, the number of publications concerning safety with PPIs have increased dramatically with many widely publicized topics appearing in high-profile journals or the media. The methodological bias of these studies, including many confounding studies and often the lack of biological plausibility, have been extensively discussed in some thoughtful reviews.[25–27] Much of the evidence, which associates PPI treatment with serious long-term conditions, is weak with very low odd ratios.[28,29] It is clear however that many of the reported adverse effects are also relevant to pediatrics,[30] especially in the long-term. PPI use potentially affects gut microbiota composition and function and decreases defense against pathogens resulting in an increased risk for infections. They

may also interfere with absorption of minerals and vitamins as well as the digestion of proteins leading to specific deficiencies and increased risks of developing bone fractures, allergic diseases, and eosinophilic esophagitis.[30,31]

Patients with GERD can also meet the diagnostic criteria for another functional disorder such as gastroparesis, since in some of them gastric emptying of liquids and/or solids is delayed.[32,33] In this patient subgroup, the esophageal exposure to acid is further enhanced thanks to the increased availability of gastric contents available for reflux.[34] More recently, electrogastrography (EGG) has been used to examine gastric pacemaker activity in children with GERD. A recent systematic review[35] found a pooled prevalence of abnormal EGG patterns in 73% of children with GERD, clearly showing that esophageal dysmotility does extend to the stomach. In addition, gastrointestinal manometry revealed significant abnormalities of antral and duodenal motility, which are associated with increased duodenogastric reflux and delayed gastric emptying.[36]

Therefore, gastrointestinal prokinetics would represent another pathophysiology-oriented therapy. However, cisapride, the only prokinetic with well-documented efficacy in GERD,[37] has been withdrawn because of its intrinsic cardiotoxicity. Metoclopramide and domperidone, besides having limited (if any) efficacy in GERD, display neurological and cardiac toxicity and are not recommended by current guidelines.[38]

Alginate-containing formulations have long been used in GERD and stood the test of time. However, advancements in the pathophysiology of reflux disease have prompted to give a new look to these "old drugs."[39] The advent of pH-impedance technology has represented a major advance, allowing us to understand that both acidic and weakly acidic reflux are implicated in symptom generation and that only those patients in whom acid is the symptom trigger respond to acid suppression. On the contrary, alginate-containing formulations achieve symptom relief regardless of the stimulus (be it acid, pepsin, bile, or mixed). This activity is likely due to the barrier effect, which translates into a reduction of the proximal migration of the refluxed gastric contents and binding and inactivation of pepsin.[39] Unfortunately, conversely from the well-established efficacy in adults, these formulations only slightly improve signs and symptoms of GERD in children and are not recommended by the joint North American and European clinical practice guidelines.[3]

Recent experimental and clinical studies have unraveled that – in patients with GERD – esophageal mucosal integrity is impaired and that this feature represents a hallmark of the disease.[40,41] Baseline esophageal impedance is now being used as a predictor of microscopic mucosal status in both adults[42,43] and children,[44,45] allowing both diagnosis and assessment of the response to therapy. Thanks to this advancement in pathophysiology, a new therapeutic strategy has recently been undertaken, that is, esophageal mucosal protection.

One of the first mucosal protective drugs was sucralfate, which is a complex of sucrose sulfate and aluminum hydroxide, originally used in the treatment of peptic ulcer. Besides adhering to the ulcer surface, it displays also several other mechanisms of action. They include inhibition of peptic digestion, mucosal protection through mucus and bicarbonate production, and stimulation of tissue growth and repair.[46] In the past, sucralfate has been extensively used in adults with GERD,[47] but with advent of PPIs, it was relegated to other gastrointestinal (GI) conditions. The available data are inadequate to determine the safety or efficacy of sucralfate in the treatment of GERD in children, particularly the risk of aluminum toxicity with long-term use. As a consequence, it is not recommended by the current guidelines.[3,4]

Besides the intrinsic activities, mucosal protective compounds should adhere to the esophageal mucosa and the contact time should be sufficient to allow their physio-pharmacologic actions to be exploited. Transit time of liquids through the esophagus is very short (less than 16 s), even in a supine subject.[48] A viscous liquid formulation that adheres to and coat the mucosa will limit the contact of refluxed acid and pepsin with the epithelial surface[49] and can act as a vehicle to deliver drugs for local action within the esophagus.[50] For this purpose, a class III medical device (namely Esoxx™ One) has been specifically developed. It contains two natural mucopolysaccharides, that is, sodium hyaluronate (obtained from bacterial fermentation by *Streptococcus equi*) and bovine sodium chondroitin sulfate, mixed to a mucoadhesive gelling agent (i.e., poloxamer 407) and a viscosity regulator compound (povidone K30) to form a mucoadhesive formulation that adheres to

the esophageal mucosa and exerts a protective effect against refluxed gastric contents, allowing mucosal healing.

The components of Esoxx are two well-known physiologic substances. Hyaluronic acid is a widespread, biologically active substance, which regulates cellular function through interaction with specific receptors.[51] It is a multifunctional, high-molecular-weight glycosaminoglycan, component of the majority of extracellular matrices and involved in several key physiologic processes, including wound repair and regeneration, morphogenesis, and matrix organization.[52] The biological roles of hyaluronic acid are in part dependent on its hydrophilic and hydrodynamic properties, which allow it to retain water and play a structural role. Indeed, hydrogels (cross-linked hydrophilic polymers) have been used as scaffolds to allow tissue repair or regeneration at sites of injury, being degraded by tissue enzymes after repair is completed.[51] Low-molecular-weight hyaluronic acid is pro-angiogenic, induces the formation of new blood vessels, and activates a signal transduction pathway leading to endothelial cell proliferation and migration. In contrast, native high-molecular-weight hyaluronic acid is anti-angiogenic and will inhibit blood vessel formation.[51] Topic hyaluronic acid formulations are employed to treat recurrent aphthous ulceration of the oral mucosa[53,54] with fast symptom relief, to which the dose-dependent anti-inflammatory activity of the compound[55] may also contribute.

Chondroitin sulfate is a natural glycosaminoglycan, present in the extracellular matrix surrounding cells, especially in the cartilage, skin, blood vessels, ligaments, and tendons, where it forms an essential component of proteoglycans.[56] Current evidence shows that chondroitin sulfate fulfills important biological functions in inflammation, cell proliferation, differentiation, migration, tissue morphogenesis, organogenesis, infection, and wound repair.[57] These effects are related to the capacity of chondroitin sulfate to interact with a wide variety of molecules including (but not limited to) matrix molecules, growth factors, protease inhibitors, cytokines, chemokines, and adhesion molecules *via* nonspecific/specific saccharide domains within the chains.[57] The compound is endowed with immune-modulatory,[58] anti-inflammatory,[57,58] and antioxidant[59] properties. Along with nonspecific interactions, chondroitin sulfate may display specific binding to bioactive molecules, such as pepsin. Peptic activity is indeed reduced both *in vitro*[60] and *in vivo*[61,62] and treatment of peptic ulcer with chondroitin sulfate has been attempted in the past.[63]

Poloxamer 407 (ethylene oxide and propylene oxide blocks) is a hydrophilic nonionic surfactant, which shows thermo-reversible properties of the utmost interest in optimizing drug formulation (fluid state at room temperature, facilitating administration and gel state above sol-gel transition temperature at body temperature, promoting prolonged release of pharmacological agents).[64] Poloxamer 407 formulations lead to enhanced solubilization of poorly water-soluble drugs and prolonged release profile for many galenic applications.[65] The poloxamer 407 adhesive properties are used to lengthen residence time of agents in the gastrointestinal tract. Good adhesion in the esophagus with efficient diffusion of the drug into the mucosa was observed in the mouse, by means of an optical fiber spectrofluorimetric method.[64]

According to European Council Directive 93/42/EEC,[66] the National Health Institute (ISS) in Rome classified this mucoadhesive formulation as class III medical device, intended for use in human beings for the purpose of treatment or alleviation of disease. Typically, the medical device function is achieved by physical means (including mechanical action, physical barrier, replacement of or support to organs or body functions, etc.).

An *ex vivo* experimental study on a swine model showed that perfusion of the esophageal lumen with this medical device is able to prevent the increase in mucosal permeability induced by acid and/or pepsin.[67] With these data at hand, two double-blind, placebo controlled studies demonstrated that short-term Esoxx treatment achieves a significant and quick symptom relief in patients with both erosive[68] and nonerosive reflux disease.[69] A randomized clinical trial found that mucosal protection *via* this medical device, added to acid suppression, improved symptoms and health-related quality of life in patients with endoscopy-negative reflux disease.[70]

All the above promising results have obtained in adults. Till now, no study with this medical device has been reported in children. In this investigation, we evaluated the efficacy and safety of a short-course treatment with Esoxx in adolescents with GERD-related symptoms.

Table 1. Qualitative and quantitative composition of Esoxx™.

Component	CAS no.	Amount (mg/10 ml)	Function
Sodium hyaluronate	9067-37-7	137.38	Active ingredient
Sodium chondroitin sulfate	24967-93-9	343.44	Active ingredient
Poloxamer 407	9003-11-6	296.76	Mucoadhesive gelling agent
Povidone K30	9003-39-8	274.76	Viscosity regulatory agent
Xylitol	87-99-0	2472.81	Sweetener
Potassium sorbate	24634-61-5	10.31	Preservative
Sodium benzoate	532-32-1	10.31	Preservative
Red grape aroma	–	2.29	Flavor-making excipient
Purified water	7732-18-5	q.s. 11.0 g	Solvent/diluent

Patients and methods

Study design

This is an investigator-initiated, retrospective, short-term study on the efficacy and safety of the Esoxx medical device in pediatric patients with dyspeptic symptoms. The study was conducted and reported according to the STROBE Guidelines[71] and care was taken to control the potential sources of biases.[72]

The clinical data of 25 patients (15 males and 10 females), median age 14.6 years (range 12–16), median body mass index 17.2 kg/m^2 (range 16–19), referred to the Pediatric Gastroenterology Unit of the University Hospital, Messina, Italy, due to the persistence of dyspeptic symptoms (such as heartburn, epigastric burning, postprandial regurgitation, and nausea) over the previous 4 weeks were reviewed. No warning symptoms or signs (such as weight loss, vomiting, dysphagia, and bleeding)[5] and no indications to perform upper gastrointestinal endoscopy[73] were present. Before beginning treatment, the patients underwent a complete physical examination and blood chemistry, including screening for celiac disease. Parents of the patients gave an informed and written consent and were asked to discontinue any other GI drug.

To each patient, 10 ml (1 stick) of Esoxx One (single dose stick formulation), to be taken after meals three times daily, was prescribed. After three consecutive weeks of treatment, patients were re-evaluated. The composition of the medical device is given in Table 1.

The trial was performed according to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), guidelines for Good Clinical Practice (GCP)[74] and the Declaration of Helsinki (1996 version, amended October 2000).[75]

The European Clinical Trials Database, launched by the European Medicines Agency, does not accept clinical trials investigating medical devices but refers to the procedures in place in the Country, where the clinical trial is conducted. Accordingly, the Study Protocol was approved by the Local Ethical Committee.

Statistical analysis

The primary endpoint was the treatment efficacy analysis, which was calculated as symptom improvement at the end of treatment. The faces pain VAS,[76] a scoring system from 0 (minimum discomfort and pain) to 10 (severe discomfort and pain), was used to rate the major GERD-related symptoms (i.e., heartburn, epigastric burning, and postprandial regurgitation) and their improvement after 3 weeks of treatment.

The secondary endpoints were safety and tolerability, assessed by recording all the adverse events,

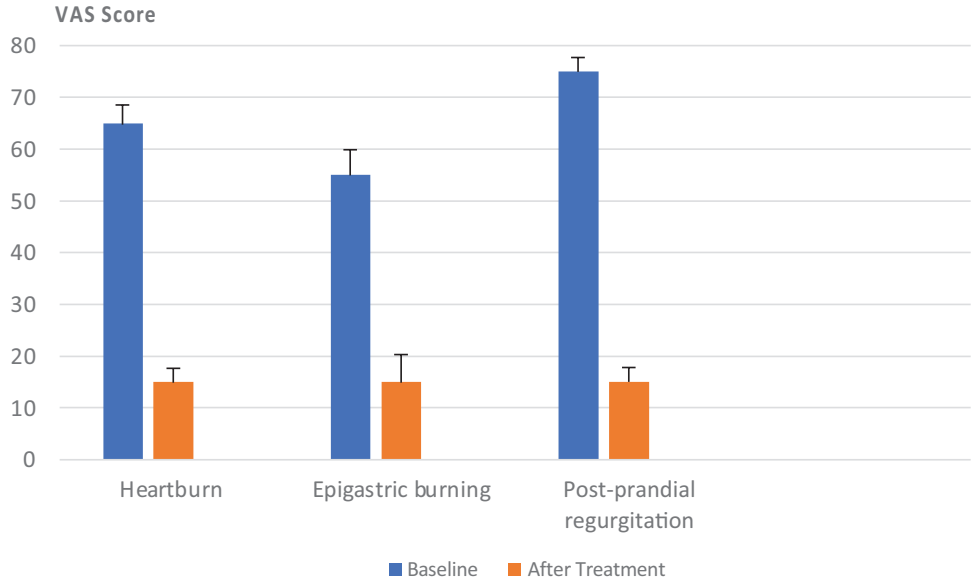

Figure 1. VAS score for the major gastroesophageal reflux disease-related symptoms in children before and after treatment with Esoxx™. Each column refers to the mean value ± SEM. All the changes were statistically significant ($p < 0.001$).

defined as any unfavorable or unintended symptom and/or sign, considered to be casually related to the medical device used.

The palatability was evaluated after each drug administration, according to a four-item scale (excellent, good, irrelevant, and bad).

Finally, patients' compliance was defined as the percentage of the test drug used, obtained by counting the returned medications at the end of treatment. A treatment compliance of 80–120% was considered acceptable.

VAS data were analyzed using a two-way analysis of variance followed by Bonferroni *post hoc* test[77] using GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA). All data are presented as the means ± SEM. A p value <0.05 was considered significant.

Results

All patients completed the treatment without adverse effects and with good tolerability and compliance. The basal VAS score for heartburn, epigastric burning, and postprandial regurgitation were 65.0 ± 3.5, 55.0 ± 4.5, and 75.0 ± 2.5, respectively. All these symptoms significantly ($p < 0.001$) improved after treatment (Figure 1). No patient required additional investigation (i.e., upper GI endoscopy), or medication (i.e., antisecretory drugs).

Discussion

The management GERD in both adults and children is still challenging, even in the third millennium.[47] The very fact that so many pharmacologic approaches have been adopted is evidence that no single drug class serves to control all the clinical manifestations of reflux disease. And indeed, there are still unmet therapeutic needs[78,79] to address which several new compounds are under active development.[47]

Over the past decades, GERD management has been dominated by antisecretory treatment, which appears to be more effective in adults than in children. However, being a chronic, relapsing disease, GERD needs often a long-term treatment and safety of acid suppression is of great concern, especially in the childhood.

Esophageal mucosal protection as therapeutic approach to GERD has been attempted in the past with not always consistent results,[80] especially due to the lack of suitable mucoadhesive formulations. The development of a specifically designed formulation to protect the esophageal lining (namely Esoxx) has been an advance in terms of

both efficacy and safety. The active ingredients are indeed two natural mucopolysaccharides. The 2020 vigilance database[81] reveals that over the past 3 years – out of a total of 4.673.192 units of Esoxx sold all over the world, 68 adverse events were recorded (i.e., an incidence of 0.001%). However, till now no data are available concerning its use in pediatric GERD. The clinical efficacy in adults prompted to evaluate the efficacy of Esoxx for GERD-related symptoms in adolescent patients, without 'red flags.' The short-term treatment (i.e., 3 week) in our patient population was effective and safe (with no treatment-related adverse events), avoiding PPI use.

A recent paper from Belgian pediatric gastroenterologists[82] has risen concern about the use of Esoxx and some other GI medical devices in children. Besides regulatory issues, the main criticism was related to the lack of qualitative and quantitative information about its composition (reported in Table 1) and the inclusion of poloxamer 407 in the oral formulation, whose special property allows to keep the hyaluronic acid and chondroitin sulfate incorporated in a gel matrix that becomes more viscous at body temperature. This viscosity increasing composition leaves a layer on esophageal mucosa during product swallowing, that is, the basis of the device effectiveness in physical barrier formation.[64] The actions of hyaluronic acid and chondroitin sulfate are merely topical, since very poor (if any) absorption of the active ingredients is likely from the macromolecular complex and both molecules are degraded within the GI tract.[83,84] Because of their thermoreversible and mucoadhesive properties, copolymers of poloxamer 407 are of growing interest for the pharmaceutical formulations.[85]

A recent investigation[86] evaluated the film forming capacity of Esoxx by using caffeine transport kinetic as a probe of barrier permeability while its protective activity was assessed by quantitating the expression of the tight junction protein, claudin-4, and the H^+ back diffusion. Compared to placebo, the caffeine passage after 15 min was significantly reduced, a difference persisting after 1 and 2 h. Tissue exposure to 0.1 HCl or simulated gastric juice (SGF) decreased claudin-4 expression (by 90% and 50%, respectively), but pretreatment with Esoxx was able to fully prevent this effect. Consequently, back diffusion of H^+ after HCl or SGF application was reduced by the mucoadhesive formulation, as shown by apical and basolateral pH-measurements.[86] These results suggest that the reduction of H^+ ions back diffusion is due to the maintenance of mucosal integrity (as mirrored by the preservation of the tight junction protein) rather than to the contribution of an acid-neutralizing effect (actually very low) of Esoxx.

A fear that long-term hyaluronic acid and chondroitin sulfate exposure might stimulate cell growth of hepatic, pancreatic, or residual cancer cells[82] is unjustified. Those concerns are rather theoretical and based mainly on experimental models.[87] Actually, hyaluronic acid is being used in tumor targeting and delivery of cytotoxic drugs.[88] A retrospective study[89] found this formulation well tolerated and effective in the symptomatic relief of radiation-induced esophagitis and a clinical trial assessing its efficacy on the incidence and severity of esophagitis in oncologic patients treated with radiotherapy or/and chemotherapy is ongoing.[90] Currently, these esophageal mucosal lesions are treated with PPIs,[22] which are systemic drugs, and a topical treatment with Esoxx (likely effective also on oral mucositis[91]) would be preferable. In any event, 2 or 3-week therapy (as performed in this study) or *on demand* treatment will be not long enough to promote the growth of any cancer, which is a multistage process over time.[92]

Esoxx was originally developed for use in adults, although the Italian National Health Institute (ISS) approved it also for use in children older than 12 years. The clinical experience in this patient population was nevertheless lacking. However, due to its innovative therapeutic approach to GERD (i.e., esophageal mucosal protection), we felt it worthwhile to explore its suitability for use in adolescents. Indeed, the assumptions to extrapolate drug efficacy to pediatric populations from adequate studies in adults[93] may well be applied to this medical device. As far as GERD is concerned, there are similar disease progressions and similar responses to intervention in the adult and pediatric populations. And the lack of systemic absorption makes pharmacokinetics virtually identical in both groups of patients, allowing in the adolescents the use of the same dose.[94]

Despite their intrinsic limitations, retrospective studies have a place in research and many of them have helped shape the clinical practices.[72] They

can represent a pilot study before starting a multicenter, placebo-controlled, RCT. Conducting a pilot prior to the main study can enhance its likelihood of success and potentially help to avoid failures.[95] On the ground of the promising results of this pilot study, we designed a double-blind, controlled trial (which is being started) to confirm Esoxx efficacy and safety in adolescents, making extrapolation from adults to children complete. Only then can this medical device enter our therapeutic armamentarium against this challenging disease.

Declarations

Ethics approval and consent to participate

The study was approved by the Local Ethical Committee and the parents of patients gave written informed consent to participate.

Consent for publication

Informed consent for publication was obtained from the parents of the patients.

Author contributions

Claudio Romano: Conceptualization; Data curation; Formal analysis; Investigation; Writing – review & editing.

Carmelo Scarpignato: Conceptualization; Funding acquisition; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Competing Interests

Professor Scarpignato is member of the Speakers' Bureau and of the Scientific Advisory Board of ALFASIGMA SpA, the marketer of Esoxx™.

Availability of data and materials

Not applicable.

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