Randomised clinical trial: mucosal protection combined with acid suppression in the treatment of non-erosive reflux disease – efficacy of Esoxx, a hyaluronic acid–chondroitin sulphate based bioadhesive formulation

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[1]See Appendix 1.

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SUMMARY

Background
Several studies have shown that patients with non-erosive reflux disease (NERD) are less responsive to proton pump inhibitors (PPIs) than those with erosive disease as they belong to different subgroups, in whom factors other than acid can trigger symptoms.

Aim
To evaluate whether combined therapy (mucosal protection plus acid suppression) would improve symptom relief compared to PPI treatment alone.

Methods
In a multicenter, randomised, double-blind trial, 154 patients with NERD were randomised to receive Esoxx (Alfa Wassermann, Bologna, Italy), a hyaluronic acid-chondroitin sulphate based bioadhesive formulation, or placebo, in addition to acid suppression with standard dose PPIs for 2 weeks. Symptoms (heartburn, acid regurgitation, retrosternal pain and acid taste in the mouth) and health-related quality of life (HRQL) were evaluated before and after treatment. The primary endpoint was the proportion of patients with at least a 3-point reduction in the total symptom score.

Results
At the end of treatment, the primary endpoint was reached by 52.6% of patients taking Esoxx compared to 32.1% of those given placebo ($P < 0.01$). The same was true also for HRQL, evaluated by means of the Short Form-36 questionnaire, which improved with both treatments, but some items were significantly better after Esoxx plus PPI therapy.

Conclusion
The synergistic effect of Essox with PPI treatment suggests that mucosal protection added to acid suppression could improve symptoms and HRQL in NERD patients.

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INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a highly prevalent disorder in Western countries, as its predominant symptom, heartburn, can occur once a week in up to 26% of the general population.[1] Despite geographical variations, the prevalence of GERD is increasing worldwide.

Over the past decade, it has been realised that there are two different phenotypes of the disease. Some patients present oesophageal mucosal lesions (i.e. erosive oesophagitis), but the majority (up to 70%) have a macroscopically normal mucosa at endoscopy. Such patients are usually considered to have non-erosive reflux disease (NERD).[2–4]

Proton pump inhibitors (PPIs) represent the first choice medical treatment for GERD,[5] in that they are able to provide an 80–85% healing rate for oesophageal lesions, including ulcers, and also reduce the incidence of complications. Pooled analyses[6, 7] have shown that in 56–76% of cases, symptom relief can also be achieved, even though this benefit seems to be reduced in patients with NERD. According to a widely quoted systematic review,[7] compared to patients with erosive oesophagitis, patients with NERD display a reduced symptom relief with PPIs, with about 20% reduction of therapeutic gain. A large AGA survey[8] found that – despite PPI use – over 55% of subjects with GERD symptoms in the general population (where non-erosive and erosive diseases are obviously mixed) report continued disruption of their quality of life.

Recent investigations have shown that not only acidic, but also non-acidic refluxes are able to induce the histopathological alterations, which have been clearly documented by electron and light microscopy in the majority of NERD patients.[9–11] In particular, the dilation of intercellular spaces between adjacent cells of the oesophageal epithelium represents a feature that has become the hallmark of microscopic oesophagitis. This intercellular gap leads to increased permeability that favours the penetration of hydrogen ions and other substances (including pepsin and bile) into oesophageal sub-mucosa, thus reaching nerve fibres, whose stimulation generates the typical symptom heartburn. Several studies[12] suggested a synergistic action between acid and duodeno-gastric reflux in inducing lesions. The important role of pepsin in the pathogenesis of extra-oesophageal manifestations of GERD is increasingly being appreciated.[13]

An ideal therapy for NERD patients should – in addition to acid secretion – address all the above-mentioned pathophysiologic features, that is provide a barrier to (and/or bind) the residual aggressive components of the refluxate (i.e. weakly acidic content and pepsin) while stimulating mucosal repair. To achieve these goals, a class III medical device, Esoxx (Alfa Wassermann, Bologna, Italy), was specifically designed and developed.[14, 15] It consists of a mixture (1:2.5 ratio) of low molecular weight (80–100 kDa) hyaluronic acid and low molecular weight (10–20 kDa) chondroitin sulphate, dispersed in a bioadhesive carrier (poloxamer 407) to form a macromolecular complex, coating the oesophageal mucosa and acting as a mechanical barrier against the noxious components of the refluxate. Transit time of liquids through the oesophagus is very short (less than 16 s), even in a supine subject.[16] A viscous liquid formulation that adheres to and coat the mucosa will limit the contact of refluxed acid and pepsin with the epithelial surface[17] and can act as a vehicle to deliver drugs for local action within the oesophagus.[18]

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.[19] 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 organisation.[20] 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.[19] 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.[19] Topic hyaluronic acid formulations are employed to treat recurrent aphthous ulceration of the oral mucosa[21, 22] with fast symptom relief, to which the dose-dependent anti-inflammatory activity of the compound[23] may also contribute.

Chondroitin sulphate 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.[24] Current evidence shows that chondroitin sulphate fulfils important biological functions in

inflammation, cell proliferation, differentiation, migration, tissue morphogenesis, organogenesis, infection and wound repair.[25] These effects are related to the capacity of chondroitin sulphate 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.[25] The compound is endowed with immune-modulatory,[26] anti-inflammatory[25, 26] and antioxidant[27] properties. Along with nonspecific interactions, chondroitin sulphate may display specific binding to bioactive molecules, such as pepsin. Peptic activity is indeed reduced both *in vitro*[28] and *in vivo*[29, 30], and treatment of peptic ulcer with chondroitin sulphate has been attempted in the past.[31]

Poloxamer 407 (ethylene oxide and propylene oxide blocks) is a hydrophilic non-ionic surfactant, which shows thermo-reversible properties of the utmost interest in optimising 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).[32] Poloxamer 407 formulations lead to enhanced solubilisation of poorly water-soluble drugs and prolonged release profile for many galenic applications.[33] The poloxamer 407 adhesive properties are used to lengthen residence time of agents in the gastrointestinal tract. Good adhesion in the oesophagus with efficient diffusion of the drug into the mucosa was observed in the mouse, by means of an optical fibre spectrofluorimetric method.[32]

According to European Council Directive 93/42/EEC,[34] the National Health Institute in Rome classified this bioadhesive 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).

An *ex vivo* experimental study on a swine model showed that perfusion of the oesophageal lumen with this medical device is able to prevent the increase in mucosal permeability induced by acid and/or pepsin.[35] With these data at hand, two double-blind, placebo-controlled studies demonstrated that short-term Esoxx treatment achieves a significant and quick symptom relief both in patients with erosive[36] or non-erosive reflux disease.[37]

In this prospective, double-blind, placebo-controlled trial the efficacy and safety of Esoxx, combined to acid suppression, vs. acid suppression alone, was evaluated in patients with NERD, diagnosed merely as endoscopy-negative reflux disease. This was selected to mirror the clinical practice, outside the referral centres, where advanced investigations are not available.

PATIENTS AND METHODS

Non-erosive reflux disease patients with typical reflux symptoms were enrolled in the study. They were of both sexes, and age ranged from 18 to 75 years. Two of the following symptoms, for example heartburn, acid regurgitation, retrosternal pain and acid taste in the mouth, should have been present from at least 3 months and at least three times per week in the month preceding the study screening visit. The diagnosis of NERD was based on the absence of macroscopic lesions of distal oesophageal mucosa at endoscopy,[3, 4] performed within 6 months from the screening visit, and by the positivity of a validated questionnaire (Reflux Disease Questionnaire, RDQ),[38] that is an RDQ score ≥8.[39] In accordance with the NICE Guidelines[40] and to avoid interference with the rapid urease test,[41] routinely performed during endoscopy, patients were free from anti-secretory medication (either a PPI or an H_2RA) for at least 2 weeks.

Exclusion criteria were the presence of erosive oesophagitis or Barrett's oesophagus, gastric or duodenal ulcer, previous gastric or major GI surgery, atopy or food intolerance, thyroid diseases, diabetes or metabolic syndrome. Moreover, pregnant, lactating or fertile women (without contraception) were also excluded.

Study design

The study was multicenter, randomised, double-blind, placebo-controlled with parallel groups. Sixteen Italian hospitals were involved, and each of them obtained the approval of the respective ethical committee.

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)[42] and the Declaration of Helsinki (1996 version, amended October 2000).[43]

Patients eligible for the study gave informed and written consent and were asked to start a 15-day (±2 days) run in/wash out period, during which any (prescription or OTC) therapy was discontinued (visit 1). The only medications permitted were antacids or alginate-containing formulations in case of symptom occurrence. At visit 2, patients were randomised – according to a computer-generated sequence – to receive one standard dose of a PPI (30 min before breakfast) + 10 mL (1 stick) of Esoxx One (single dose stick formulation) or placebo (with the same

taste and viscosity, packed in identical, sequentially numbered, containers) q.d.s., that is 1 h after each daily meal, and at bedtime for a 14-day treatment period. The allocation sequence was generated by LB Research (contract research organisation), while enrolment and assignment of participants to a given treatment were performed by the principal investigator of the study centres (see Appendix 1). During the study period, daily symptom diaries, recording the presence or absence of each symptom during the day and the night, were filled by each patient. Before (visit 2) and after this short course of therapy (visit 3), frequency and severity of NERD symptoms were evaluated using the same RDQ questionnaire. Health-related quality of life (HRQL) was also assessed using the SF-36 questionnaire.[44] Both questionnaires were administered by physicians, who were unaware of the treatment given. Results of each item were compared with those of published data for the Italian normative sample.[45] Pre- and post-treatment results for each item were also compared. The study design and the detailed assessment schedule can be found in the Table S1.

Safety and tolerability were assessed by recording all the adverse events, defined as any unfavourable or unintended symptom and/or sign, considered to be casually related to the drug(s) used in the study. The palatability was evaluated after each drug administration, according to a 4-item scale (excellent, good, irrelevant and bad). Hence, there were 4 per day × 15 days evaluations for each patient.

Finally, patients' compliance was defined as the percentage of the test drug used, obtained by counting the returned medications at visit 3. A treatment compliance of 80–120% was considered acceptable.

The European Clinical Trials Database (EudraCT), launched by the European Medicines Agency (EMA), 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 Clinical Trial Protocol was registered (Protocol code: Esoxx-NERD/001/2012) at the Italian Ministry of Health, and the beginning of the trial (i.e. the inclusion of the first patient), as well as the end of the trial (i.e. the last evaluation of the last included patient), was notified to the regulatory authorities.

Statistical analysis

The primary endpoint was the treatment efficacy analysis, which was calculated as the proportion of patients with at least 3-point reduction of the total symptom score (TSS). This was calculated by collecting and computing the intensity of each patient's symptom (on the basis of the RDQ questionnaire at the final visit) and comparing it with the baseline values, obtained at the end of the run in/wash out period (visit 2). Typical symptoms were evaluated according to a 5-degree Likert scale[46]: 0 = no symptom, 1 = poorly troublesome symptoms, 2 = troublesome symptoms, 3 = very troublesome symptoms, interfering with daily activities, 4 = intolerable symptoms, not permitting any daily activity.

There were four different secondary endpoints: (i) number of patients with 50% reduction of TSS at final visit, (ii) number of patients with TSS reduction at the final visit, (iii) change TSS after treatment and (iv) HRQL physical and mental items according to the SF-36 questionnaire, which were calculated via a web-based program[47] and presented as radar plots or spidergrams.[48] Changes in the severity and frequency of each symptom (heartburn, acid regurgitation, retrosternal pain, acid taste in the mouth) were also evaluated.

The intention-to-treat (ITT) population included all randomised patients, who took at least one dose of medication while per protocol (PP) analysis was performed on all randomised patients, who concluded the treatment, with an adequate compliance rate and without any protocol violation. The former analysis was used to evaluate the primary endpoint and the latter for both primary and secondary endpoints. The safety population included all randomised patients, who took at least one dose of the study drugs.

Chi-squared and Fisher's exact test, two tails, were used to compare percentages of values for primary and secondary endpoints, while arithmetic means and frequencies were assessed by means of 95% confidence intervals (CIs).[49] All the calculations were performed using the PRISM 6.0 software (GraphPad, San Diego, CA, USA), running on a MAC.

The sample size was calculated on the basis of the reduction of NERD TSS by 3 points at final visit and assuming a rate of 10% improvement in the placebo group and 30% in the Esoxx arm. A power level of 80% with a significance value ≤0.05 (two-sided Fisher's exact test) required a sample size of 70 patients for each group. Taking into account a 12% of non-evaluable patients, the sample was raised to 80 patients. The estimation was made, using the STATA (Version 13, StataCorp LP, College Station, TX, USA) for MAC.

RESULTS

In the 16 centres involved in the study, 172 NERD patients were screened and 154 out of them were randomised to treatment, 76 in the Esoxx group and 78 in

the placebo one. Among them, 18 patients were considered dropouts for various reasons: eight for adverse events, two for treatment failure and eight denied consent (Figure 1).

Table 1 shows the baseline demographics and the clinical characteristics of the groups studied, in the ITT population. There were no statistical differences among the different characteristics of the recruited patients in the two arms.

The compliance, defined as mean number (±s.d.) of sticks taken, was similar (P = NS) in the two arms of treatment, that is 90.9 ± 22.9 vs. 90.2 ± 20.7 in the Esoxx and placebo groups, respectively.

As regards the primary endpoint, Table 2 (ITT analysis) shows that the proportion of patients with TSS reduction of at least 3 points at final visit was higher in the Esoxx than in the placebo group and the difference was always significant. Also the proportion of patients with 50% TSS reduction at visit 3, as secondary endpoint, resulted to be significantly higher ($P < 0.042$) in the Esoxx (38.2%) than in the placebo (23.1%) group (Table 2). In addition, number of patients with TSS reduction at the final visit was significantly higher in Esoxx than in placebo arm ($P < 0.026$). Finally, TSS after treatment improved more with Esoxx than with placebo treatment ($P < 0.011$). Similar results were obtained in the PP population (Table S2). As shown in Table 3, all the symptoms evaluated subsided with both treatments, but the amelioration of heartburn and especially regurgitation was more marked with Esoxx combined with

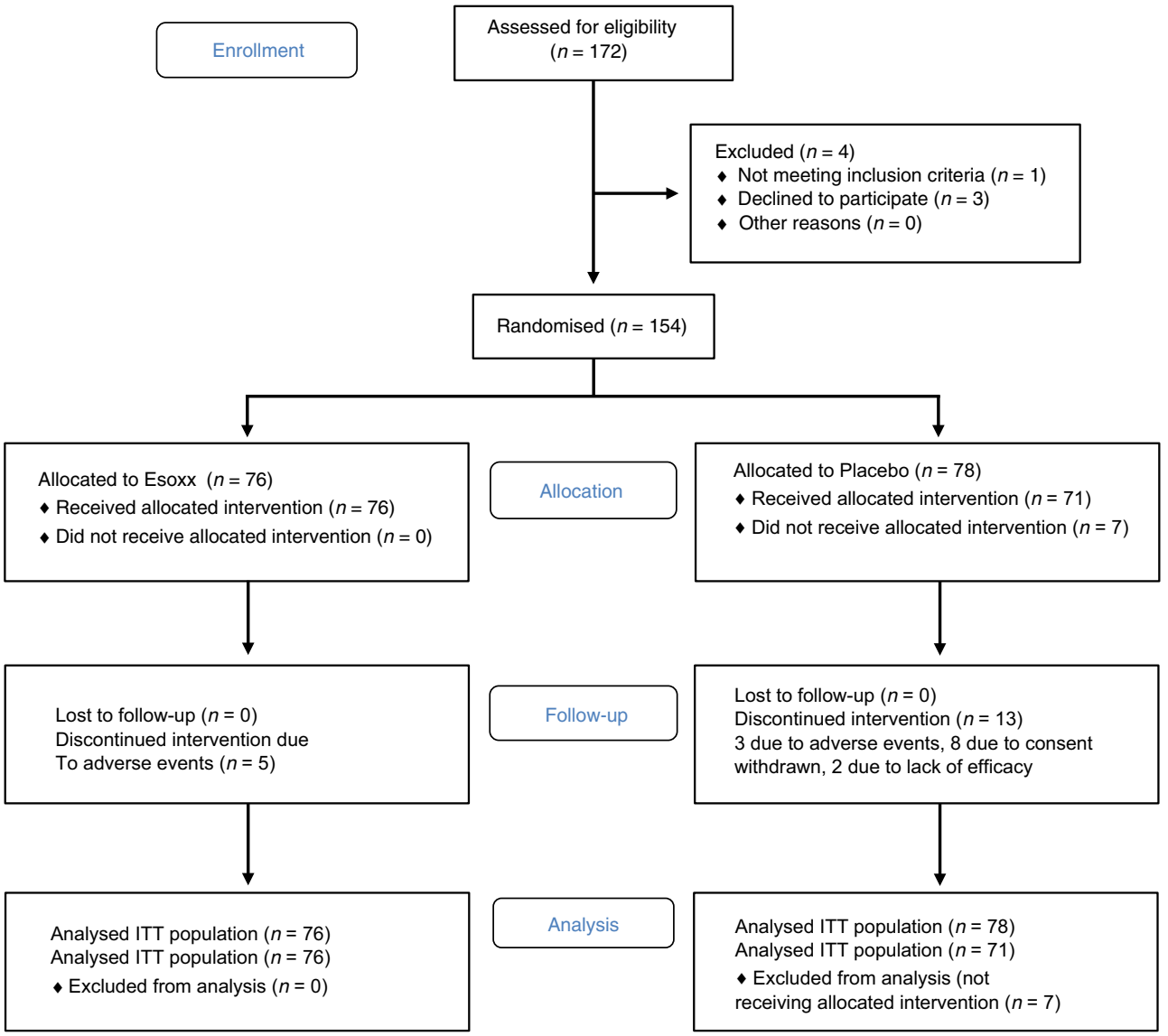

Figure 1 | Consort 2010 flow diagram.

Table 1 | Baseline characteristics of NERD patients receiving Esoxx or placebo, combined with PPIs

	Esoxx (n = 76)	Placebo (n = 78)	P value
Female, *N* (%)	48 (63.2%)	46 (59.0%)	NS
Age (years), mean ± s.d.	45.45 ± 14.98	45.51 ± 13.37	NS
Range (min–max)	18–81	24–75	
BMI (kg/m^2)	23.87 ± 3.10	23.77 ± 3.23	NS
GERD total symptom score	7.30 ± 2.4	7.19 ± 2.6	NS
Proportion of patients with ≥3 GERD symptoms (%)	44.0	41.0	NS
Heartburn	84.2	85.9	
Retrosternal pain	53.9	49.3	
Acid regurgitation	69.7	66.2	
Acid taste in the mouth	60.5	59.2	
Past treatment with PPIs (%)	56.6	64.8	NS
Past treatment with other anti-GERD therapies (%)	23.7	29.6	NS

Table 2 | Effect of Esoxx, combined with PPI therapy, on primary and secondary endpoints in patients with NERD: ITT analysis

	PPI + Esoxx		PPI + Placebo		
Trial endpoints	*n/N*	%	*n/N*	%	P value
Primary					
No of patients with TSS reduction of at least 3 points	40/76	52.6	25/78	32.1	0.01
Secondary					
No of patients with 50% reduction of TSS	29/76	38.2	18/78	23.1	0.042
No of patients with TSS reduction at final visit	60/76	78.9	44/78	56.4	0.003
TSS (±s.d.) before and after treatment	Before	After	Before	After	
	8.53 ± 2.6	5.42 ± 2.1	8.03 ± 2.7	6.49 ± 2.6	
Change (±s.d.) in TSS	−3.11 ± 3.1		−1.54 ± 3.0		0.002

TSS, total symptom (heartburn, retrosternal pain, regurgitation, acid taste) score.

PPIs. The therapeutic gain with Esoxx was 20.5%, 15.3% and 10.2% for TSS (symptom severity), heartburn and regurgitation incidence, respectively.

Finally, the quality of life, evaluated by means of the SF-36 items, improved with both treatments (Figure 2). Indeed, 2 weeks after therapy the SF-36 items become closer to those of the Italian normative sample.[45] However, the improvements in General Health Perception and the Social Function items were significantly ($P < 0.01$ and $P < 0.02$, respectively) better after Esoxx plus PPI therapy.

The safety of Esoxx was very good, as the total number of adverse events was similar to that of placebo and there were no serious adverse events in any treatment arms (Table 4). The most frequent manifestations pertained to the gastrointestinal tract (nausea, flatulence, bloating, dyspepsia, etc.) and respiratory organs (cough, rhinitis, pharyngeal disorders) (Table 5).

On the basis of the total number of evaluations collected (n = 7230), in 92% of Esoxx administrations, palatability was considered acceptable, independently of the intake time (be it during the day or at bedtime) while the same held true for 90% of placebo administrations (P = NS). The distribution of these evaluations is shown in Figure 3.

DISCUSSION

The results of this study show that, when mucosal protection is added to acid suppression, a significantly higher number of NERD patients obtained symptom relief with combination therapy. Indeed, both the primary and secondary endpoints were achieved in a larger proportion of subjects.

Although PPIs are effective in obtaining symptom relief in both erosive and NERD,[50] their efficacy for the relief of regurgitation is modest, and considerably lower than that achieved for heartburn.[51] In addition, although not as frequent as previously suggested,[7] PPI-refractory heartburn, occurring more commonly in NERD than in erosive disease, does exist. Some 20% (range 15–27%) of correctly diagnosed and

Table 3 | Effect of Esoxx, combined with PPI therapy, on (a) severity and (b) frequency of GERD symptoms in patients with NERD: ITT analysis

	PPI + Esoxx, mean score ± s.d.			PPI + placebo, mean score ± s.d.			
Symptom	Before therapy	After therapy	Adjusted mean change (95% CI)	Before therapy	After therapy	Adjusted mean change (95% CI)	*P* value Esoxx vs. placebo
(a)							
Heartburn	1.80 ± 1.1	0.72 ± 0.8	−1.131 (−1.340 to −0.922)	1.99 ± 1.0	1.09 ± 1.0	−0.836 (−1.034 to −0.638)	0.0319
Regurgitation	1.84 ± 1.1	0.64 ± 0.8	−1.095 (−1.280 to −0.911)	1.53 ± 1.1	0.94 ± 1.0	−0.685 (−0.861 to −0.509)	0.0009
Retrosternal pain	1.36 ± 1.2	0.42 ± 0.7	−0.852 (−1.023 to −0.682)	1.15 ± 1.2	0.59 ± 0.8	−0.612 (−0.775 to −0.449)	0.0323
Acid taste in the mouth	1.53 ± 1.1	0.63 ± 0.8	−0.754 (−0.968 to 0.541)	1.3 ± 1.1	0.8 ± 1.0	−0.494 (−0.696 to −0.291)	0.0623
(b)							
Heartburn	3.08 ± 1.7	1.38 ± 1.5	−1.719 (−2.083 to −1.354)	3.23 ± 1.5	1.94 ± 1.6	−1.229 (−1.578 to −0.883)	0.0408
Regurgitation	2.92 ± 1.7	1.23 ± 1.5	−1.562 (−1.892 to −1.233)	2.60 ± 1.8	1.63 ± 1.7	−1.021 (−1.332 to −0.710)	0.0128
Retrosternal pain	2.14 ± 1.8	0.82 ± 1.3	−1.232 (−1.511 to −0.952)	1.86 ± 1.7	1.03 ± 1.3	−0.896 (−1.163 to −0.630)	0.0676
Acid taste in the mouth	2.57 ± 1.7	1.16 ± 1.5	−1.285 (−1.640 to 0.930)	2.38 ± 1.8	1.53 ± 1.7	−0.876 (−1.213 to −0.540)	0.0790

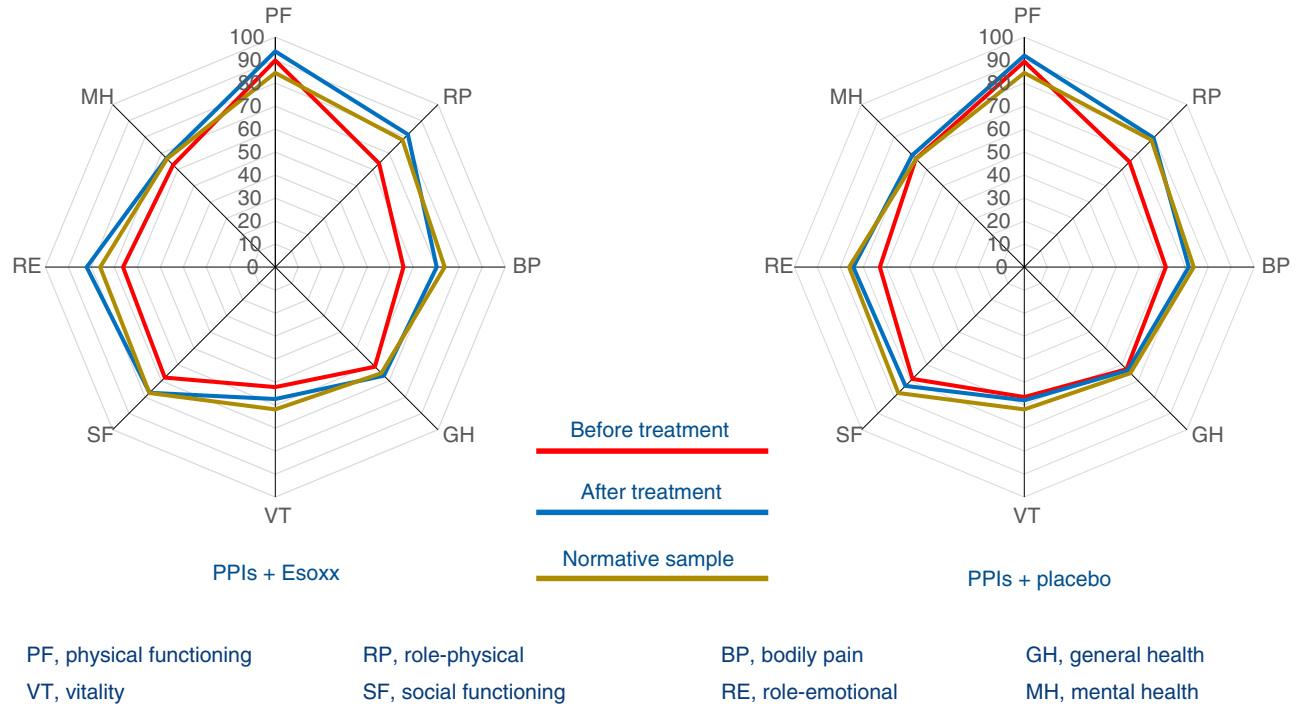

Figure 2 | HRQL measured in NERD patients before and after 2-week treatment with Esoxx or Placebo combined to PPIs. Note that, after treatment, the SF-36 items are close to those of the Italian normative sample.

appropriately treated patients do not respond to PPI therapy at standard doses.[52]

Various underlying mechanisms have been shown to contribute to the failure of PPI treatment. They include patient-related (e.g. lack of compliance), physician-related (e.g. misdiagnosis) and drug-related (e.g. short duration of action) mechanisms.[53, 54] At the present time, much current research is focused on weakly acidic reflux[55] and oesophageal hypersensitivity.[56] The pH-impedance technique has been increasingly used to explore the underlying pathophysiology in PPI-resistant patients. Several groups of investigators have indeed shown that weakly acidic reflux plays a major role in PPI-resistant erosive and non-erosive disease.[57]pH-impedance monitoring has also

Table 4 | Adverse events in NERD patients, included in the ITT analysis, receiving PPI + Esoxx or PPI + placebo

	Esoxx (n = 76)	Placebo (n = 71)	P value
Total number of unique AEs	32	14	NS
Total number of AEs	35	20	NS
Total number of patients with at least one AE	18 (23.7)	11 (15.5)	NS
Total number of unique drug-related AEs	23	13	NS
Total number of drug-related AEs	24	19	NS
Total number of patients with at least one related AEs	13 (17.1)	10 (14.1)	NS
Total number of serious AEs	0	0	NS
Total number of patients with at least one AE leading to discontinuation	5 (6.6)	3 (3.8)	NS

Values within parenthesis are expressed as percentage. AE, adverse event.

Table 5 | Patients, treated with PPI combined with Esoxx or placebo, with at least one TEAEs classified for system organ class (SOC) – safety analysis

SOC	Esoxx (n = 76)	Placebo (n = 71)
Patients with at least one TEAE	18 (23.7)	11 (15.5)
Gastrointestinal disorders	13 (17.1)	7 (9.9)
Respiratory, thoracic, mediastinal disorders (cough, rhinitis, throat irritation, pharyngeal disorders)	4 (5.3)	1 (1.4)
Nervous system disorders (dysgeusia, headache, migraine)	3 (3.9)	–
Cardiac disorders (palpitations, tachycardia)	1 (1.3)	1 (1.4)
Ear and labyrinth (vertigo)	1 (1.3)	–
General disorders (hypertension)	1 (1.3)	–
Infections and infestations	1 (1.3)	3 (4.2)

Values within parenthesis are expressed as percentage.

allowed identification of a previously unknown subgroup of patients, namely those with normal oesophageal pH-impedance recording, but a positive association between symptoms and non-acidic reflux episodes, that is patients who are hypersensitive to non-acidic reflux.[57] Finally, this methodology has enabled a better differentiation between patients with NERD and those with functional heartburn.[58] It is therefore evident that different patient subgroups belong to NERD, which is indeed an umbrella term. Among them, only patients with true NERD or acid hypersensitive oesophagus (now called reflux hypersensitivity, according to the Rome IV criteria[59]) are expected to display a satisfactory symptomatic response to acid suppression therapy with a PPI. On the contrary, subjects hypersensitive to non-acid reflux or those with functional heartburn (which – together with reflux hypersensitivity – does not pertain anymore to the realm of GERD) will obviously be nonresponsive to anti-secretory drugs.[60]

In patients with NERD, who are refractory to a correctly performed PPI therapy, the lack of symptom relief could be due to persistence of microscopic mucosal alterations induced by weakly acidic reflux,[61] by pepsin or other components of the refluxate[62] and underlined by an impaired mucosal integrity.[63] Current pharmacologic approaches to address this clinically challenging condition are limited. Reflux inhibitors represent a promise unfulfilled,[64] effective prokinetics are lacking [65] and antidepressants, despite being effective in selected patients,[66] give rise to adverse events in up to 32% of patients.[67]

A better approach to patients with NERD should be therefore making a more precise diagnosis, by adding a functional evaluation (e.g. pH or pH-impedance recording) to negative endoscopy. When this has been done, the estimated complete symptom response rate after PPI therapy appeared comparable to that observed in patients with GERD.[68] Including biopsy (and subsequent histology) of the 'macroscopically normal' mucosa during endoscopic examination[61] would be ideal. It is evident, however, that this approach, being time-consuming and costly, is not achievable in the everyday clinical practice.

An alternative, easier, approach could be combination therapy, that is adding drugs with different mechanism (s) of action to PPIs. Up to now, only irsogladine (a mucosal protective compound)[69] and alginate-containing formulations[70, 71] – given as add-on medications – proved to be capable of improving symptom control in NERD patients. The addition of mosapride (a prokinetic compound) to PPIs does not add any benefit[72, 73] unless NERD patients display a delay in gastric emptying.[74]

The mucosal protective device, Esoxx, was shown to be capable of achieving a significant and quick symptom relief in patients with NERD in this and a previous trial.[37] Its amelioration of regurgitation severity and frequency is of clinical interest, taking into account the negligible effect

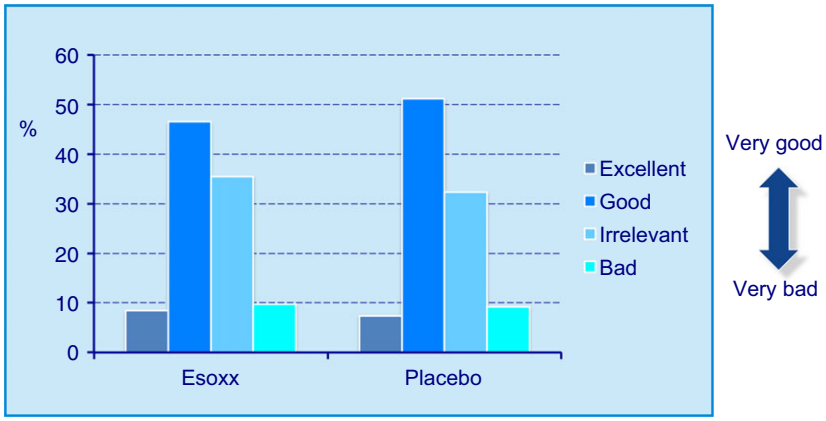

Figure 3 | Palatability assessment of Esoxx or placebo formulations, used in the present study. Distribution of the 60 evaluations for each patient.

PPIs have on this cardinal symptom of reflux disease.[51, 63] As shown by a small study,[36] this formulation may well be effective also in patients with erosive disease, in whom its protective and reparative properties would favour healing of oesophageal mucosal lesions.

The synergistic effect of Esoxx with PPIs, shown in this study, suggests that mucosal protection, routinely added to acid suppression, could extend to a larger number of patients with NERD both symptom relief and improvement of HRQL, thus reducing the incidence of treatment failures. PPIs achieve a symptom relief, which increases over time both in erosive and non-erosive disease. This has been further shown by the studies comparing PPIs (namely esomeprazole) with P-CABs (namely linaprazan).[75, 76] It may well be that this combined approach achieves at 2 weeks the same symptom relief, obtained with PPIs at 4 weeks. However, for those patients asking for quick symptom relief, this time-dependent therapeutic gain could be worthwhile from their own perspective.

The present study has intrinsic limitations. As functional investigation (i.e. pH-impedance recording) was not performed, the population studied included patients with functional heartburn and reflux hypersensitivity. In addition, although adequately powered to show a significant effect, this was a relatively small trial. A larger study in patients with PPI-resistant NERD as well as a trial in patients with extra-oesophageal symptoms is worthwhile.

Despite recent research has established the sites and mechanisms underlying oesophageal mucosal defence, its enhancement is very rarely pursued in clinical practice. Drugs able to strengthen mucosal defence do exist, but they have not been studied in well designed clinical trials.[63] Due their high efficacy in reflux disease, it is unlikely that these drugs represent a real alternative to PPIs. However, their use in less severe disease or as add-on medications to PPIs could be useful. Furthermore, used in the long term, these mucosal protective compounds might prolong remission and delay relapse.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Study design and assessment schedule.

Table S2. Effect of Esoxx, combined with PPI therapy, on primary and secondary endpoints in patients with NERD: PP analysis.

AUTHORSHIP

Guarantor of the article: C. Scarpignato.

Author contributions: According to the International Committee of Medical Journal Editors (JCMJE), Carmelo Scarpignato and Vincenzo had full access to all of the data in the study and take the responsibility for the integrity of the data. Carmelo Scarpignato, Vincenzo Savarino performed study concept and study design and drafted the manuscript; Carmelo Scarpignato, Vincenzo Savarino and Fabio Pace analysed and interpreted the data and critically revised the manuscript for important intellectual content; LB Research (Claudio Iannacone) and Carmelo Scarpignato performed statistical analysis; Carmelo Scarpignato obtained funding; LB Research (Sara Bellasio) performed administrative, technical or material support; and Antonella Ferrieri performed study supervision. All authors approved the final version of the manuscript.

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The company did not have any role in the execution of the study or interpretation of data. The terms of the financial support included freedom for the authors to reach their own conclusions, and an absolute right to publish the results of their work, irrespective of any conclusions reached.

Declaration of personal interests: Vincenzo Savarino is member of the Speakers' Bureau of Alfa Wassermann, the manufacturer of Esoxx. Fabio Pace has no conflict of interests to disclose. Carmelo Scarpignato is member of the Speakers' Bureau and of the Advisory Board of Alfa Wassermann.

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APPENDIX 1
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How Efficacious is Ziverel® for Symptomatic Relief of Acute Radiation-Induced Esophagitis? Retrospective Study of Patients Receiving Oncologic Treatment

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Abstract

Objective: To evaluate the efficacy of ZIVEREL® for symptomatic relief in a retrospective cohort of patients with acute radiation-induced esophagitis receiving oncologic treatment with radiotherapy alone or radiochemotherapy.

Introduction: ZIVEREL® is a new oral medical device composed of hyaluronic acid, chondroitin sulfate, and poloxamer 407. Radiation-induced esophagitis is a dose-limiting toxicity in oncologic treatment with radiotherapy or radiochemotherapy, and sometimes a limiting factor for treatment.

Material and Methods: Between February 2016-July 2017, we evaluated 41 patients (33 men and 8 women) treated with ZIVEREL®, with a diagnosis of lung cancer (63.41%), gastric cancer (31.71%), and esophageal cancer (4.88%) who developed acute radiation-induced esophagitis (CTCAE grade 1 [60.98%] and grade 2 [39.02%]) during treatment with radiotherapy alone (36.59%) or radiochemotherapy (63.41%). The median age was 69 years (range, 38 to 90 years).

Results: Of the total number of patients, 38 (92.68%) experienced an improvement of their symptoms; 13 of these patients (34.21%) had previously received support treatment, according to usual clinical practice, compared with 3 patients (7.32%) in whom ZIVEREL® did not lead to an improvement in symptoms. ZIVEREL® was prescribed as initial treatment (41.46%), after initiation of support treatment (34.15%), or together with support treatment (24.39%). Of the 41 patients treated, 39 patients (95.12%) completed the oncologic treatment satisfactorily, and it was necessary to interrupt oncologic treatment in only 2 cases (4.88%) of total number of patients.

Conclusion: ZIVEREL® is well tolerated and plays a key role in the symptomatic relief of radiation-induced esophagitis resulting from oncologic treatment.

Keywords: Acute esophagitis; Chemotherapy; Chemoradiotherapy; Chondroitin sulfate; Hyaluronic acid; Poloxamer 407; Radiotherapy; Radiochemotherapy; ZIVEREL®

Abbreviations: COX-2: Cyclooxygenase-2; CTCAE: Common Terminology Criteria for Adverse Events; DNA: Deoxyribonucleic Acid; ECM: Extracellular Matrix, Gy: Gray; IL-1β: Interleukin 1 Beta; NFκB: Nuclear Factor Kappa Beta; PGE2: Prostaglandin E2; RT: Radiotherapy; RT-CH: Chemoradiotherapy; TNF-α: Tumor Necrosis Factor Alpha

Introduction

The esophagus is a tube composed of muscle and membranous tissue. It extends from the pharynx (upper border of the cricoid cartilage, 15 cm from the incisors) to the stomach and is closed at the ends by the contraction of 2 sphincter muscles. It serves to transport food from the mouth to the stomach and has no major secretary function. In terms of anatomy, the esophagus comprises 3 sections: the cervical section (5-6 cm), the thoracic section (20 cm), and the abdominal section (2-3 cm). In terms of histology, it is composed of 4 functional layers:

i. The mucosa, which is composed of stratified squamous epithelium;

ii. The submucosa, which is formed by loose connective tissue that supports the mucosal layer;

iii. The muscularis propria, which is in turn formed by a circular layer and a longitudinal layer and is responsible for voluntary and involuntary movements of the esophagus;

iv. The adventitia, which is composed of highly vascularized supportive connective tissue and is surrounded by mesothelium in the abdominal portion [1].

In the context of oncologic treatments, the fact that the esophagus covers 3 anatomical regions means that it can be

irradiated in various clinical situations and is sometimes difficult to protect. Both palliative treatment and curative treatment with ionizing radiation between C6 and T12 are associated with partial irradiation of the esophagus.

Radiation-induced esophagitis is an acute, dose-limiting toxicity in oncologic treatment. Since it can lead to interruption of treatment, hospitalization, and even death, clinicians should be aware of this condition as an adverse effect of oncologic therapies, in order to prevent interruption of treatment, as it has been associated with reduced survival [2,3]. The pathogenesis of radiation-induced esophagitis is complex and not well defined. However, there is sufficient evidence that the symptoms are caused by lesions affecting the structure of the epithelium and that they are induced by the action of ionizing radiation on the esophageal mucosa, with rupture of double-stranded DNA [4], formation of reactive oxygen species [5], over expression of proinflammatory cytokines [6,7] and bacterial overgrowth on ulcerated lesions [8]. Clinically, acute esophagitis includes dysphagia, odynophagia, nausea, anorexia, and retrosternal pain. If these symptoms are severe, they can lead to dehydration, malnutrition, and weight loss [9,10].

ZIVEREL® is a new, over-the-counter medical device that comes as an oral solution in a 10-ml stick pack. It is composed of hyaluronic acid, chondroitin sulfate, and poloxamer 407 and plays a role in the symptomatic relief of esophagitis induced by radiotherapy alone or radiochemotherapy in oncologic patients. ZIVEREL® acts naturally and exerts a protective action by reinforcing the effect of the elements that make up the extracellular matrix, where the connective tissue provides the architecture, proteoglycans maintain the fluid-electrolyte balance, and glycoproteins maintain the intracellular substrate responsible for cell–cell reactions and cell–matrix reactions.

Hyaluronic acid is a glycosaminoglycan formed by glucuronic acid and N-acetylglucosamine disaccharide units. It is found mainly in the extracellular matrix of the loose connective tissue and is associated with several key processes, including cell signaling and repair, as well as with tissue generation, morphogenesis, and structural organization of the extracellular matrix itself [11]. In clinical terms, its role is well known in conditions such as mouth ulcers, where its barrier effect relieves symptoms [12,13]. Chondroitin sulfate forms part of the glycosaminoglycan group in the extracellular matrix, which is in turn formed by D-glucuronic acid and N-acetylgalactosamine. It has been shown to protect the epithelium of the esophageal mucosa by shielding the epithelial areas damaged by acid, thus diminishing catabolic activity and inhibiting proteolytic enzymes (e.g., metalloproteases, collagenase, or elastase). Chondroitin sulfate also regulates several inflammatory mediators (TNF-α, IL-1β, COX-2, PGE2, and NFκB) and reduces the synthesis of nitric oxide, which is involved in the inflammatory cascade [14,15]. Polaxamer 407 is a bioadhesive component that acquires the consistency of gel at body temperature, thus ensuring that the active ingredients of ZIVEREL® adhere to the damaged mucosa and are not dragged away by ingestion of food and liquids [16].

The objective of this study was to evaluate whether administration of ZIVEREL® diminishes the grade of acute radiation-induced esophagitis and the incidence of severe esophagitis in oncologic patients treated with radiotherapy or radiochemotherapy.

Material and Methods

Between February 2016 and July 2017, we retrospectively evaluated 41 patients diagnosed with cancer (lung, gastric and esophageal cancer). The patients had received radiotherapy alone (RT) or radiochemotherapy (RT-CH) and developed acute radiation-induced esophagitis grade 1 or 2 according to the most recent CTCAE criteria [10]. Their support treatment included ZIVEREL®. The patients were evaluated weekly during treatment with RT or RT-CH and until 2 weeks after the end of treatment.

Results

Table 1: Patient characteristics.

Parameter	No. (%)
Sex	
Men	33 (80.49%)
Women	8 (19.51%)
Age in years	
Median	69
Range	38-90
Cancer diagnosis	
Esophageal cancer	13 (31.71%)
Lung cancer	26 (63.41%)
Stomach cancer	2 (4.88%)
Treatment received	
RT	15 (35.59%)
RT-CH	26 (63.41%)
Dose (Gy)	
Median	55.8
Range	25-66

RT: radiotherapy; RT-CH: radiochemotherapy; Gy: Gray

We analyzed data from 41 patients (33 men [80.49%] and 8 women [19.51%]), of whom 26 (63.41%) were diagnosed with lung cancer, 13 (31.71%) were diagnosed with esophageal cancer, and 2 (4.88%) were diagnosed with gastric cancer. The median age was 69 (range, 38-90) years. A total of 15 patients received radiotherapy alone (36.59%) and 26 received radiochemotherapy (63.41%). The median dose was 55.8 Gy (range, 25-66 Gy) (Table 1). Of the 41 patients who received treatment with ZIVEREL®, 16 (39.02%) started treatment with ZIVEREL® when they developed grade 2 acute radiation-induced esophagitis and 25 (60.98%) when they developed grade 1 esophagitis. ZIVEREL® was administered daily during treatment

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once a day (10 mL [4.88%]), twice a day (20 mL [58.54%]), or 3 times a day (30 mL [36.58%]), depending on the usual clinical practice of the prescribing physician, for a minimum of 4 weeks (Table 2).

Table 2: ZIVEREL® treatment.

Parameter	No. (%)
Esophagitis grade (baseline)	
I	25 (60.98%)
II	16 (39.02%)
Dose (mL/day)	
10	2 (4.88%)
20	24 (58.54%)
30	15 (36.58%)
Timing	
Initial treatment	17 (41.46%)
Support treatment	10 (24.39%)
Adjuvant treatment	14 (34.15%)

Support treatment was indicated according to usual clinical practice, and, depending on the intensity of the symptoms, the patients received proton pump inhibitors, anti-inflammatory drugs, analgesics, anti-H2 antagonists, antacids, and/or opioids. Of the 41 patients studied, symptoms improved in 38 patients (92.68%) and did not improve in 3 (7.32%) after treatment with ZIVEREL®. Of the patients whose symptoms improved, 13 (34.21%) had started support treatment before administration of ZIVEREL®. ZIVEREL® was the first product used for symptomatic relief of grade 1 and 2 esophagitis in 17 patients (41.46%) and was administered without further support treatment. It was prescribed with support treatment in 10 patients (24.39%) according to the usual clinical practice of the prescribing physician. In 14 patients (34.15%), ZIVEREL® was used as an adjuvant to the initial support treatment after no improvement was observed with the initial medication (Figure 1).

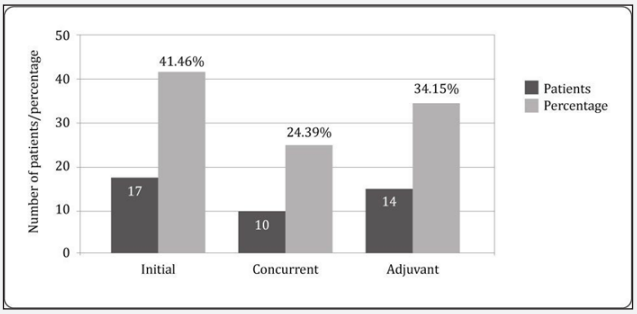

Figure 1: Timing for ZIVEREL®.

a. Initial: ZIVEREL® without support treatment;

b. Concurrent: ZIVEREL® with support treatment;

c. Adjuvant: ZIVEREL® together with support treatment after no improvement was observed with the initial medication.

Of the 17 patients (41.46%) who received ZIVEREL® as their initial treatment, 7 did not require subsequent support treatment. Five of the 7 patients had a diagnosis of acute grade 1 esophagitis when the drug was indicated, and ZIVEREL® was prescribed in the remaining 2, who had a diagnosis of grade 2 esophagitis. Of the total number of patients, 39 (95.12%) completed radiotherapy and radiochemotherapy satisfactorily. Oncologic treatment had to be interrupted in only 2 cases (4.88%) owing to acute toxicity, which took the form of grade 3 esophagitis, although in both cases, a curative dose for the type of tumor treated was reached. Three of the 41 patients (7.32%) studied had to be admitted to hospital with acute grade 3 radiation-induced esophagitis. No adverse reactions to ZIVEREL® were reported. The drug was well tolerated by all those patients it was prescribed to.

Discussion

As stated above, acute esophagitis caused by oncologic treatment is a common finding and a dose-limiting factor for oncologic treatment. Therefore, clinicians should be aware of this adverse effect in order to prevent interruption of radiotherapy or radiochemotherapy, as this has been associated with reduced overall survival, because the patient cannot receive the intended treatment optimally [2,3].

Appropriate diagnosis of the symptoms of acute radiation-induced esophagitis is hampered by several factors, including infection of the esophagus, whose symptoms mimic those of esophagitis and which can be affected by oncologic treatment. Infection can lead the esophagus to lose its barrier function, thus facilitating local invasion by commensal microorganisms and pathogens and gastro esophageal reflux before initiation of treatment [8]. Therefore, correct evaluation of the patient before support treatment is prescribed is essential in order to rule out esophageal candidiasis and oropharyngeal mucositis, which can lead to an erroneous initial diagnosis. In our study, all patients were exhaustively assessed in order to identify those who had concurrent infection, oropharyngeal mucositis, gastroesophageal reflux, or any other condition that could mask or mimic the symptoms of acute radiation-induced esophagitis.

In our study, most of the patients analyzed (95.12%) completed their oncologic treatment satisfactorily. As explained above, the timing for ZIVEREL® varied, and the product was indicated as initial treatment in 41.46% of patients, together with support treatment in 24.39%, and as an adjuvant to initial treatment in 34.15% (Figure 1). Similarly, dosing of ZIVEREL® differed depending on the usual practice of the prescribing physician (once a day [10 mL] in 4.88%, twice a day [20 mL] in 58.54%, and 3 times a day [30 mL] in 36.58%). Limited experience with this product in our setting was one of the reasons why dosing of ZIVEREL® varied from patient to patient. According to results from patients with gastroesophageal reflux the optimal dose is 4 sachets per day (40 mL/day) [12], although we found that symptoms improved with a lower dose in 63.42% of patients. It remains unclear if ZIVEREL®, whether taken alone or in combination with support treatment and

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administered according to usual clinical practice, helps to ensure completion of the oncologic treatment prescribed, which is clearly associated with better outcomes and increased survival [17,18]. Therefore, determination of the optimal dose for symptomatic relief in these patients would provide relevant data and thus make it possible to establish the best dosing regimen for the control of the symptoms of acute esophagitis induced by oncologic treatment, regardless of the support treatment prescribed. Similarly, nonsteroidal anti-inflammatory drugs are a cornerstone of symptomatic treatment, although these are contraindicated in many patients owing to comorbid conditions or drug interactions; therefore, they should be avoided where possible [19]. Thus, it would be interesting to determine the role of ZIVEREL® as a support treatment for these groups of patients with acute esophagitis after radiotherapy or radiochemotherapy.

As mentioned above, the esophagus covers 3 anatomical regions. Therefore, ionizing radiation, whether palliative or curative, administered between C6 and T12 could partially affect the esophageal mucosa. The patients we studied were diagnosed with lung cancer (63.41%), esophageal cancer (31.71%), and gastric cancer (4.88%). Radiotherapy-related factors that play a role in acute toxicity include volume of irradiated tissue, total dose received, daily dose, total treatment time, irradiation technique, and concurrent systemic therapy [20,21]. When systemic therapy is administered concomitantly with radiotherapy, the symptoms of acute esophagitis appear a week earlier than when treatment is administered sequentially. Furthermore, a greater percentage of patients are unable to complete their initially planned treatment, and the risk of associated death is greater [22].

The radiotherapy dosing parameters that best define onset of acute esophagitis remain unclear. Several studies have evaluated the effect of the dose-volume histogram (DVH) on the probability of acute and late complications affecting the esophagus. The most widely studied dosing parameters include the absolute volume, mean dose (D_{mean}), the percentage of volume that receives the reference dose (V_{dose}), or the maximum dose (D_{max}) delivered to the esophagus. A systematic review of the literature [23] showed that the best studied predictors, and those for which most evidence is available with respect to radiation-induced esophagitis, were D_{mean}, V_{20}, V_{30}, V_{40}, V_{45}, and V_{50}. Improved radiotherapy technology has led to a reduction in the incidence and severity of esophagitis, thus demonstrating that older techniques based on 2D planning led to increased acute and chronic adverse effects [24]. New techniques have made it possible to treat the target volume more accurately, thus limiting the dose that reaches healthy tissue, including the esophagus [25]. Given that our study was performed at a single center, the radiotherapy technology available was homogeneous for all the patients included, with the only differences being in the dose per fraction and the total dose administered. Therefore, all of the study patients were susceptible to developing acute esophagitis induced by oncologic treatment, since treatment planning included a considerable volume of the esophagus within the treatment field.

Similarly, adding chemotherapy to the radiotherapy schedule increases the frequency of esophagitis by approximately 5-fold [26], whereas treatment with radiotherapy alone with curative intent leads to significantly lower rates of grade 3 or higher esophagitis [27]. We found that 15 patients (35.59%) received treatment with radiotherapy alone and 26 patients (63.41%) received treatment with radiochemotherapy with curative intent. All of the patients who were admitted to hospital (3 patients, 7.32%) or whose oncologic treatment was interrupted (2 patients, 4.88%) owing to acute associated toxicity, were receiving treatment with radiochemotherapy. This observation leads us to ask whether patients who received radiotherapy and chemotherapy concurrently would benefit from early administration of support therapy or intensification thereof and thus be able, where possible, to complete the prescribed treatment appropriately.

The role of radio protectors in the development of esophagitis induced by oncologic treatment has been studied in recent years. The role of amifostine in particular is controversial, and the drug has been evaluated in several studies, with contradictory results. Some authors reported a reduced frequency of acute esophagitis with this therapy [28], whereas others found no benefit of combining amifostine with radiochemotherapy [29]. Amifostine was also a poorly tolerated and highly emetogenic. At present, data are insufficient to recommend daily use of amifostine for prevention of esophagitis induced by ionizing radiation. However, other agents (e.g., glutamine) have proven successful as prophylaxis of radiation-induced esophagitis [30], and a significant reduction in the incidence of acute radiation-induced esophagitis has been shown in patients who received treatment with glutamine [31]. In our study, we have not observed any side effects secondary to the administration of ZIVEREL®. Therefore, we can conclude that ZIVEREL® is a safe and well-tolerated product that may have an important role in the management of acute esophagitis in patients receiving oncologic treatment with radiotherapy alone or radiochemotherapy.

Conclusion

ZIVEREL® is a well-tolerated and safe product that plays a major role in the symptomatic relief of patients with acute esophagitis induced as a consequence of oncologic treatment. Initial data must be confirmed in new, well-designed prospective studies in which ZIVEREL® is uniformly administered in a homogeneous cohort of patients.

Conflict of Interest

No potential conflicts of interest relevant to the present article were reported.

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