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Efficacy of Esophageal Protector in Treating Gastroesophageal Reflux Disease with Extraesophageal Symptoms: a Multicenter, Open-Label, Observational Study

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Aim: to assess effects of esophageal protector Alfasoxx on extraesophageal symptoms in patients with GERD.
Materials and methods. A prospective open multicenter post-registration observational study was conducted. The study included 546 patients aged 6 to 85 years (the average age of patients is 42.4 ± 16.9 years) with a verified diagnosis of GERD (endoscopically and/or pH-metrically), the presence of extraesophageal symptoms of the disease (according to the results of an objective examination and consultations of specialists), to whom the attending physician prescribed a course of treatment with a medical device Alfasoxx in accordance with the instructions for medical use. The patients were recruited by 51 researchers in 26 cities of Russia. The study in chronological order consisted of a screening visit and two recorded visits (the observation period within the framework of the use of the Alfasoxx esophagoprotector). The screening visit was conducted on the day of the patient's admission. Visit 1 could be conducted on the same day as the screening visit, whereas visit 2 was conducted 4–5 weeks after visit 1 at the end of the course of treatment.
Results. According to the results obtained, at the end of the study, 42.7 % (95 % CI: 38.5–46.9) had complete disappearance of extraesophageal GERD symptoms (questionnaire RSI = 0 points). When comparing the average values of the total RSI score before and after treatment, there was also a statistically significant regression from 13.8 points (95 % CI: 13.2–14.4) at visit 1 to 2.0 points (95 % CI: 1.8–2.2) at visit 2. Thus, the decrease in the total score was significant and exceeded 80 % of the initial value. When analyzing the dynamics of individual indicators of the RSI scale before and after treatment, a significant regression in the severity of all symptoms of the disease was noted. In addition, the results showed that the proportion of patients taking antacid-containing drugs at visit 1 significantly decreased from 58.2 % (95 % CI: 54.0–62.4) to 15.2 % (95 % CI: 12.1–18.3) by visit 2. The average score on the Likert scale of satisfaction with treatment was 4.8 (95 % CI: 4.8–4.9), whereas the convenience of using Alfasoxx is 4.7.
Conclusion. This prospective observational multicenter study demonstrated that the addition of Alfasoxx to standard GERD therapy contributes to a significant regression of both esophageal and extraesophageal symptoms, as well as a decrease in the need for antacid medications.
Keywords: gastroesophageal reflux disease; extraesophageal symptoms; esophagoprotector
Conflict interest. The observational study was conducted with the support of Alfasigma Rus.
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Эффективность эзофагопротектора в лечении гастроэзофагеальной рефлюксной болезни с внепищеводной симптоматикой: результаты открытого наблюдательного многоцентрового исследования

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Цель. Изучение влияния эзофагопротектора «Альфазокс» на экстраэзофагеальные симптомы у пациентов с ГЭРБ.

Материалы и методы. Проведено проспективное открытое многоцентровое пострегистрационное наблюдательное исследование. В исследование были включены 546 пациентов в возрасте от 6 до 85 лет (средний возраст больных 42,4 ± 16,9 года) с верифицированным при эндоскопии и/или pH-метрии диагнозом ГЭРБ и наличием у них экстраэзофагеальных симптомов болезни согласно результатам объективного обследования и консультаций специалистов. Лечащим врачом назначен курс лечения медицинским изделием «Альфазокс» (комбинации гиалуроновой кислоты и хондроитина сульфата) в соответствии с инструкцией по медицинскому применению. 51 исследователь в 26 городах России проводил набор пациентов. Исследование в хронологическом порядке состояло из визита скрининга и двух регистрируемых визитов (период наблюдения в рамках применения эзофагопротектора «Альфазокс»). Визит скрининга проводили в день поступления пациента. Визит 1 мог быть проведен в тот же день, что и визит скрининга, тогда как визит 2 — через 4–5 недель после визита 1 по окончании курса лечения. Во время каждого визита исследователь заполнял форму карты пациента (опросник RSI, опросник оценки частоты и тяжести пищеводных симптомов, опросник оценки пациентом удовлетворенности лечением по 5-балльной шкале Лайкерта).

Результаты. Согласно полученным результатам по завершении исследования у 42,7 % (95 % ДИ: 38,5–46,9) отмечалось полное исчезновение экстраэзофагеальных симптомов ГЭРБ (опросник RSI = 0 баллов). При сравнении средних значений суммарного балла RSI до и после лечения также был отмечен статистически значимый регресс с 13,8 балла (95 % ДИ: 13,2–14,4) на визите 1 до 2,0 балла (95 % ДИ: 1,8–2,2) на визите 2. Таким образом, снижение показателя суммарного балла было значительным — более чем на 80 % от исходного значения. При анализе динамики индивидуальных показателей шкалы RSI до и после лечения отмечен достоверный регресс выраженности всех симптомов заболевания. Доля пациентов, принимавших антацидсодержащие препараты на визите 1, значимо сократилась с 58,2 % (95 % ДИ: 54,0–62,4) до 15,2 % (95 % ДИ: 12,1–18,3) к визиту 2. Средний балл по шкале Лайкерта удовлетворенностью лечением составил 4,8 (95 % ДИ: 4,8–4,9), средний балл по шкале Лайкерта удовлетворенностью удобством применения «Альфазокса» — 4,7 (95 % ДИ: 4,6–4,7).

Вывод. Настоящее проспективное наблюдательное многоцентровое исследование продемонстрировало, что добавление Альфазокса к стандартной терапии ГЭРБ способствует достоверному регрессу как пищеводной, так и внепищеводной симптоматики, а также снижению потребности в приеме антацидных препаратов.

Ключевые слова: гастроэзофагеальная рефлюксная болезнь, внепищеводные симптомы, эзофагопротектор

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Introduction

According to a contemporary view, gastroesophageal reflux disease (GERD) is an esophageal disorder caused by impaired motor-evacuation function of the gastroesophageal zone that leads to spontaneous and regularly repeated retrograde passage of the gastric and/or duodenal contents into the esophagus [1, 2]. GERD pathophysiology is multifactorial and consists of heterogeneous morphofunctional impairments including dysfunction of lower esophageal sphincter, increased frequency of transient lower esophageal sphincter relaxation, hiatus hernia, esophageal dysmotility, as well as disorders of gastric motor function [3–5].

At present GERD is one of the most frequent reasons to seek medical help in primary care settings in many countries, which is explained by high prevalence of the disease in the global population [3, 6]. Based on latest data of the Global Burden of Disease Study (1990–2017), there is a significant increase in worldwide number of reported cases of the disease, i.e., from 424 million cases (95 % CI: 372–477) up to 709 million cases (95 % CI: 626–795) [7]. In their latest meta-analysis that included data from 102 trials, Nirwan J.S. et al. (2020) have shown that global prevalence of GERD comprises 13.98 % (95 % CI: 12.47–15.56) [8]. The highest prevalence of GERD is seen in North America (19.55 %, 95 % CI: 15.60–23.83), while the lowest prevalence is reported in Asian countries (12.92 %, 95 % CI: 10.51–15.53) [8]. As shown in a recently published multicenter study that evaluated prevalence of GERD symptoms in visitors of Russian polyclinics with the help of Mayo Clinic questionnaire, disease frequency comprised 34.2 % in a large respondent sample (n = 6132) [9].

GERD is characterized by a chronic recurrent pattern of symptoms that significantly and adversely affects patients' quality of life [3, 10, 11]. Heartburn, belching and regurgitation are seen as typical clinical signs of the disease; however, in some cases GERD is manifested by complex atypical symptoms known as extraesophageal syndromes [11–13]. According to the global Montreal Consensus (2006), cough, laryngitis, bronchial asthma, as well as erosion of dental hard tissues of reflux etiology are extraesophageal syndromes that are significantly associated with GERD [14]. Multiple systematic reviews and meta-analyses have confirmed the correlation between GERD and the mentioned disorders [15–18]. In the ProGERD study that was the largest prospective, multicenter cohort study (n = 6215), extraesophageal symptoms were detected in 32.8 % of patients with heartburn [19]. A study in Italy has shown that 74.4 % of patients with GERD have at least one extraesophageal symptom, and laryngeal symptoms are seen in a large proportion of patients (19.9–38.7 %) [20]. Similar results were obtained in the USA where 26 % of patients presented both signs of GERD and laryngeal symptoms [21]. During 11-year follow-up in this country, there was almost 5-fold increase in number of visits to otolaryngologists due to laryngopharyngeal reflux [22].

According to current recommendations, antisecretory therapy with proton pump inhibitors (PPIs) is the first line therapy to induce and maintain remission in patients with GERD [1, 2, 23, 24]. Nevertheless, efficacy of therapy with PPIs is suboptimal in patients with extraesophageal symptoms. In particular, it was established that about 50 % of patients did

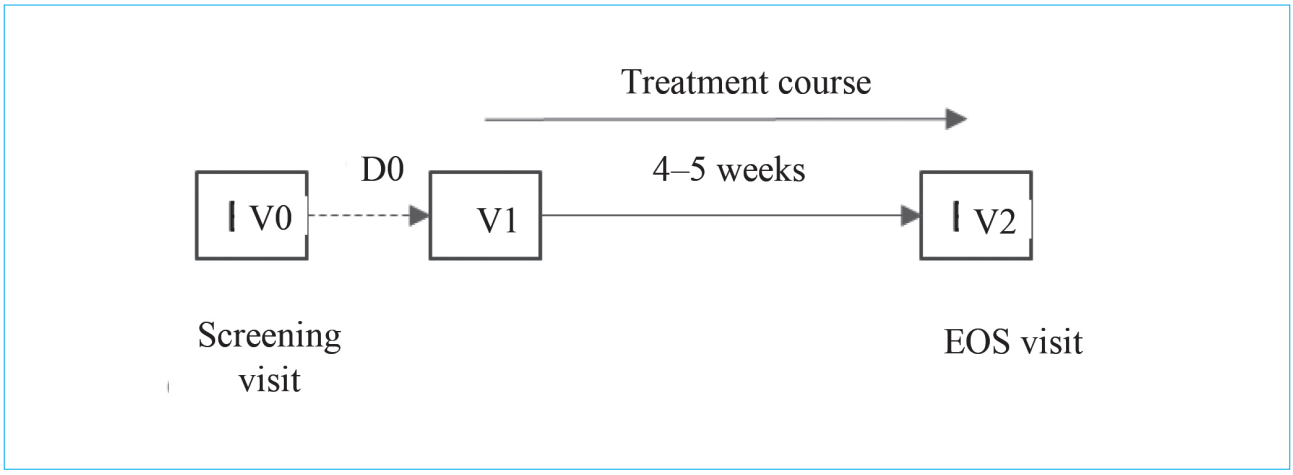

Fig. 1. Study design

not achieve any therapeutic response within 8–12 weeks of treatment, while 15 % had only a partial response [25, 26]. Moreover, PPIs affect only pathophysiological vector associated with hydrochloric acid production and do not alleviate adverse effects of other components of the refluxate (including pepsin and bile) on esophageal and laryngeal mucosae [27]. With this background, it is reasonable to assess efficacy of esophageal protector Alfasoxx that coats esophageal mucosa and acts as a mechanical barrier against damaging factors when used in complex therapy in patients with extraesophageal symptoms of GERD [28].

This study was performed to assess effects of esophageal protector Alfasoxx on extraesophageal symptoms in patients with GERD.

Materials and methods

Study design

It was a multicenter, prospective, open-label, postmarketing, observational study assessing effects of Alfasoxx on extraesophageal symptoms in patients with GERD. The study included patients with a verified (by endoscopy and/or measuring pH) diagnosis of GERD, presenting extraesophageal symptoms of the disease (based on results of physical examination and medical advice), who were prescribed with a course of treatment with Alfasoxx according to labeling information. Patients were enrolled by 51 investigators in 26 Russian cities.

In this study patients were observed only during treatment with esophageal protector Alfasoxx. At the end of treatment period, a patient completed his / her participation in the study. Chronologically, the study consisted of a screening visit and two recorded visits (follow-up during treatment with esophageal protector Alfasoxx). The screening visit was performed on patient's admission day. Visit 1 could take place on the same day as the screening visit, while visit 2 was performed at 4–5 weeks after visit 1 at the end of treatment period (see Fig. 1). During each visit the investigator completed a case report form (CRF).

Inclusion and exclusion criteria

To be included into the study a patient must meet all criteria below:

- age not less than 6 years;
- verified diagnosis of GERD;
- extraesophageal symptoms of GERD (any other reason for comorbidity should be ruled out);
- treatment with Alfasoxx prescribed by a physician according to indications for use;
- informed consent form signed by the patient for enrollment and personal data processing.

The patient could not be included or must be excluded from the study if any of the exclusion / withdrawal criteria below were met:

- Barrett's esophagus;
- malignant neoplasms;
- gastric or duodenal ulcer at present or during previous year;
- history of hypersensitivity to or intolerability of hyaluronic acid, chondroitin sulfate or poloxamer 407;
- pregnancy, breastfeeding or women of childbearing potential not using contraception;
- participation in any other clinical study at present or within previous 30 days;
- any other medical and nonmedical reasons that, in physician's opinion, may hamper patient's participation in the study.

Study endpoints

Primary endpoints:

• proportion (%) of patients with completely resolved extraesophageal symptoms after treatment with Alfasoxx (RSI = 0 points).

Secondary endpoints:

• mean difference in score by RSI questionnaire used to assess frequency and severity of extraesophageal symptoms of GERD prior to and after treatment;

• mean difference in total score by the questionnaire used to assess frequency and severity of esophageal symptoms of GERD prior to and after treatment;

• assessment of frequency of antacids use as needed during the follow-up period;

• assessment of patient's satisfaction with treatment using a 5-point Likert scale.

Ethical issues

The study was prepared and conducted in compliance with legal, regulatory and industry standards and applicable ethical principles. The study protocol (version 1.4) was approved by the decision of the Independent Interdisciplinary Ethics Committee for Ethical Review of Clinical Studies (extract from the minutes No. 10 of the meeting held on June 11th, 2021).

Statistical data processing

Statistical data processing was performed using specialized software Statistica 10.0. Primary and secondary analyses are presented as descriptive statistics. For continuous variables description, mean arithmetic, standard deviation and 95 % confidence intervals were calculated. Categorical variables were presented as frequency percentage. Appropriate types of ANOVA repeated measures were used to assess the significance of observed differences, normally distributed data. Wilcoxon test was used in case of any other distributions. A chi-square test or Fisher's exact test was used to assess the significance of differences in categorical variables. Analysis of primary and secondary endpoints was based on the ITT-population (intention-to-treat). Differences between the groups were considered significant at $p < 0.05$.

Results

Study population

The study included a total of 598 patients, however based on results of medical records review, data on 52 patients were excluded from subsequent analysis (missing critical data for analysis). The final sample included 546 patients aged 6–85 years (mean age: 42.4 ± 16.9 years).

The study population was diagnosed based on pooled clinical findings (99.82 %), results of esophagogastroduodenoscopy (90.84 %), PPI response testing (63.19 %), pH measuring (8.97 %) and pH-impedance monitoring (1.10 %). There were more patients with nonerosive reflux disease (47.80 %) compared to patients with reflux esophagitis (44.52 %). 7.69 % of medical records contained no clear information about endoscopic classification of the disease (procedure was not performed for objective reasons). Examination by an otolaryngologist (83.88 %), cardiologist (27.29 %) and pulmonologist (25.82 %) was the most common way to rule out any other underlying reasons for extraesophageal symptoms in patients with GERD. As a rule, any therapy received prior to patient's enrollment included PPIs (84.25 %), antacids (14.10 %) and prokinetics (10.26 %). In this study mean treatment duration was 28.8 ± 2.9 days, with frequency of esophageal protector administration — 3.7 ± 0.5 times a day.

Treatment efficacy

Extraesophageal symptoms. A validated RSI questionnaire was used to track score changes between study visits 1 and 2 and to assess treatment efficacy in improving extraesophageal symptoms. 100 % of patients had extraesophageal symptoms because it was one of the inclusion criteria. Upon completion of the treatment course and follow-up period, a total number of patients with completely resolved extraesophageal symptoms, i.e., zero total score on the RSI scale, was calculated. Based on the results, at the end of the study 42.7 % (95 % CI: 38.5–46.9) of patients with GERD achieved complete resolution of extraesophageal symptoms (score on the RSI scale = 0 points) (see Fig. 2). Comparison of mean total scores on the RSI scale prior to and after the treatment revealed a statistically significant improvement from 13.8 points (95 % CI: 13.2–14.4) at visit 1 up to 2.0 points (95 % CI: 1.8–2.2) at visit 2 (see Fig. 3). Thus, a total score decreased markedly, by more than 80 % of the baseline value. Analysis of changes in individual scores on the RSI scale prior to and after the treatment revealed a significant improvement of all disease symptoms (see Table).

Esophageal symptoms. Simultaneously with tracking changes in extraesophageal symptoms, during the study, frequency and severity of esophageal symptoms of GERD were recorded and analyzed, based on the total score obtained with the help of the rating scale for frequency

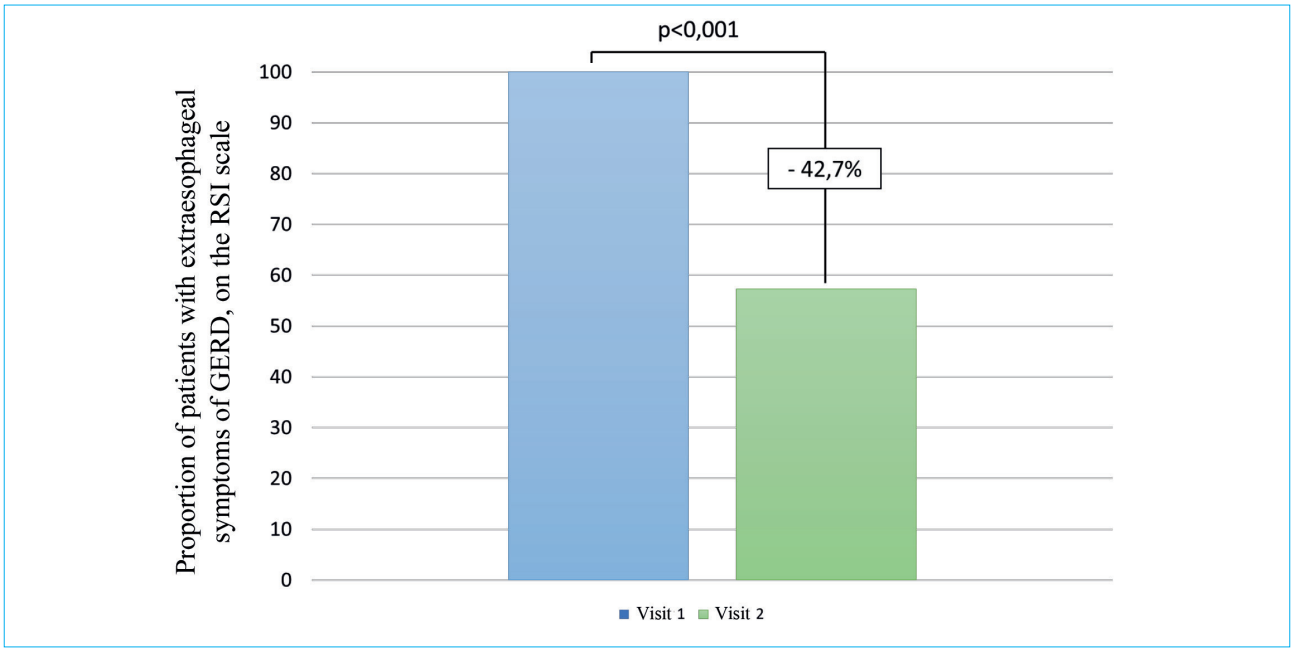

Fig. 2. Proportion of patients with extraesophageal symptoms of GERD, on the RSI scale

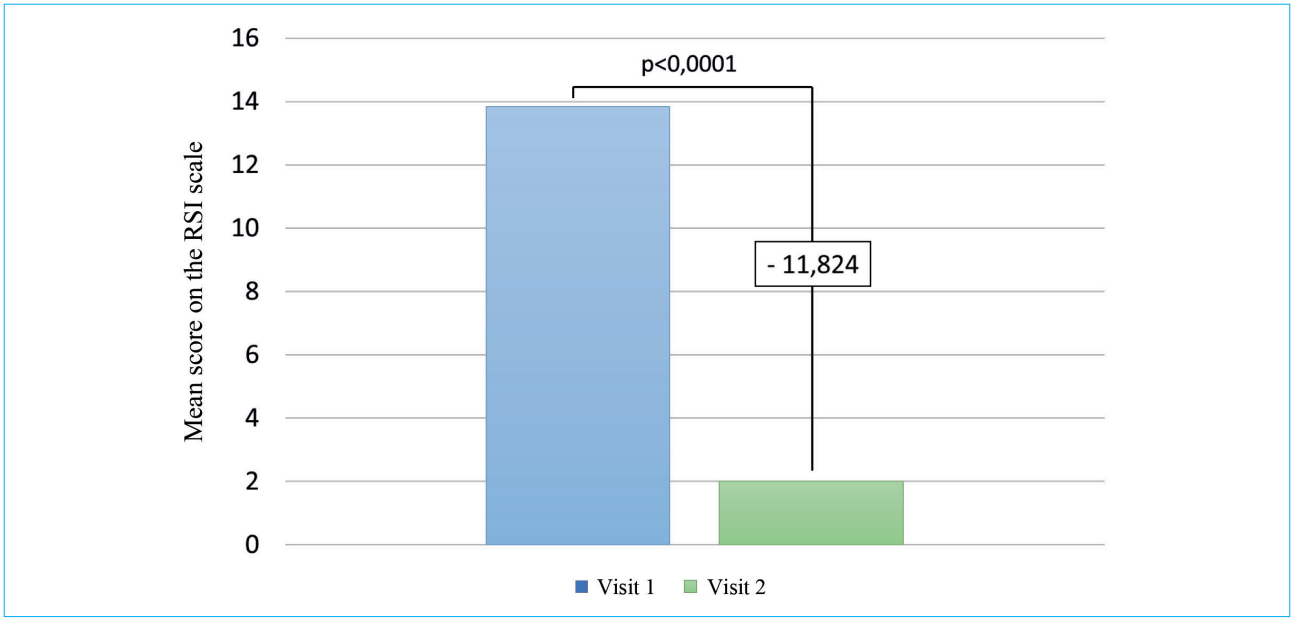

Fig. 3. Mean score changes on the RSI scale

and severity of the symptoms. The severity of each extraesophageal symptom within the week prior to assessment was evaluated using a 5-point Likert scale, where 0 = absent symptom, 1 = slightly bothering symptom, 2 = bothering symptom, 3 = significantly bothering symptom that hampers daily activities, 4 = intolerable symptom that prevents from performing daily activities. The frequency of a symptom within the week prior to assessment was evaluated using the following scale: 0 = 0 days per week, 1 = 1 day per week, 2 = 2–3 days per week, 3 = 4–7 days per week. For each symptom, numerical score was calculated as "symptom severity" x "symptom frequency", with maximum score = 12 points. For each patient, obtained points were summed up: Σ points = Σ numerical score for each symptom, with maximum total score = 72 points. In general population mean total score at visit 1 equaled to 17.2 points (95 %

Table. Changes in individual symptoms on the RSI scale

Symptom	Visit 1, mean score	Visit 2, mean score	Changes, mean score	*p*
1. Hoarseness or voice alterations	1,45 ± 1,28	0,19 ± 0,48	-1,26 ± 1,23	<0,0001
2. Cough, tickling sensation	1,70 ± 1,24	0,33 ± 0,59	-1,37 ± 1,20	<0,0001
3. Mucus production or postnasal drip	1,75 ± 1,34	0,35 ± 0,64	-1,40 ± 1,26	<0,0001
4. Difficulty in swallowing solid or liquid substances / tablets	0,96 ± 1,16	0,09 ± 0,33	-0,87 ± 1,12	<0,0001
5. Coughing fits after the meal or in lying position	1,71 ± 1,36	0,22 ± 0,50	-1,49 ± 1,32	<0,0001
6. Difficulty in breathing or shortness of breath / laryngospasm	0,62 ± 1,09	0,04 ± 0,20	-0,58 ± 1,05	<0,0001
7. Prolonged coughing fits	1,49 ± 1,41	0,21 ± 0,56	-1,28 ± 1,32	<0,0001
8. Sensation of a lump or foreign body in the throat	1,71 ± 1,41	0,27 ± 0,53	-1,44 ± 1,29	<0,0001
9. Heartburn, burning sensation behind the sternum, in esophageal area, retrosternal pain, dyspepsia	2,43 ± 1,37	0,31 ± 0,60	-2,12 ± 1,35	<0,0001

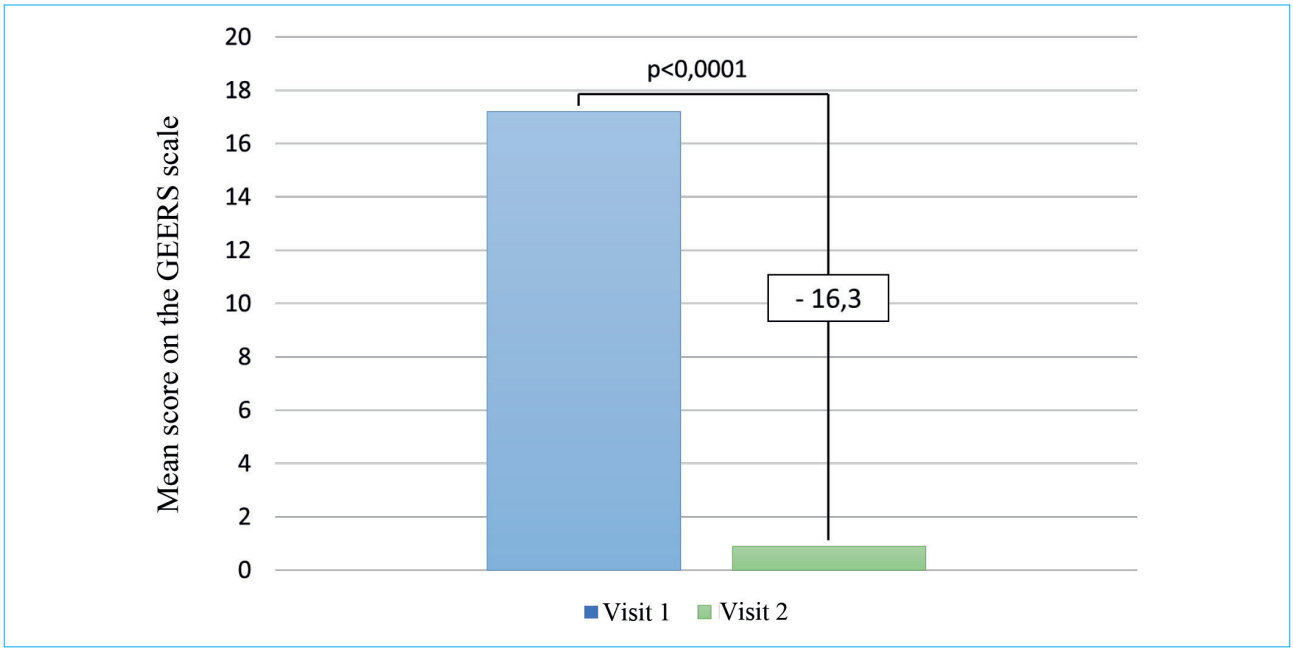

Fig. 4. Changes in mean scores on the rating scale for frequency and severity of the symptoms

CI: 16.1–18.3) with subsequent reduction to 0.9 point (95 % CI: 0.7–1.0) at visit 2 (see Fig. 4). Thus, a total score decreased markedly, by more than 90 % of the baseline value.

Need for antacid-based therapy. During the study, we tested a hypothesis on possible reduction in antacids intake frequency in patients receiving Alfasoxx. According to obtained results, a proportion of patients administering antacids at visit 1 decreased significantly: from 58.2 % (95 % CI: 54.0–62.4) to 15.2 % (95 % CI: 12.1– 18.3) by visit 2 (see Fig. 5)

Treatment satisfaction and convenience of dosage regimen. At visit 2, patients were asked to assess treatment satisfaction and convenience of dosage regimen of the prescribed esophageal protector (Alfasoxx) using a 5-point Likert scale. According to obtained results, patients reported a high level of these integral indicators. In particular, mean score for treatment satisfaction on the Likert scale was 4.8 points (95 % CI: 4.8–4.9), while convenience of Alfasoxx dosage regimen scored 4.7 points (95 % CI: 4.6–4.7) (see Fig. 6).

Safety. During the study, no adverse events were reported by the physicians.

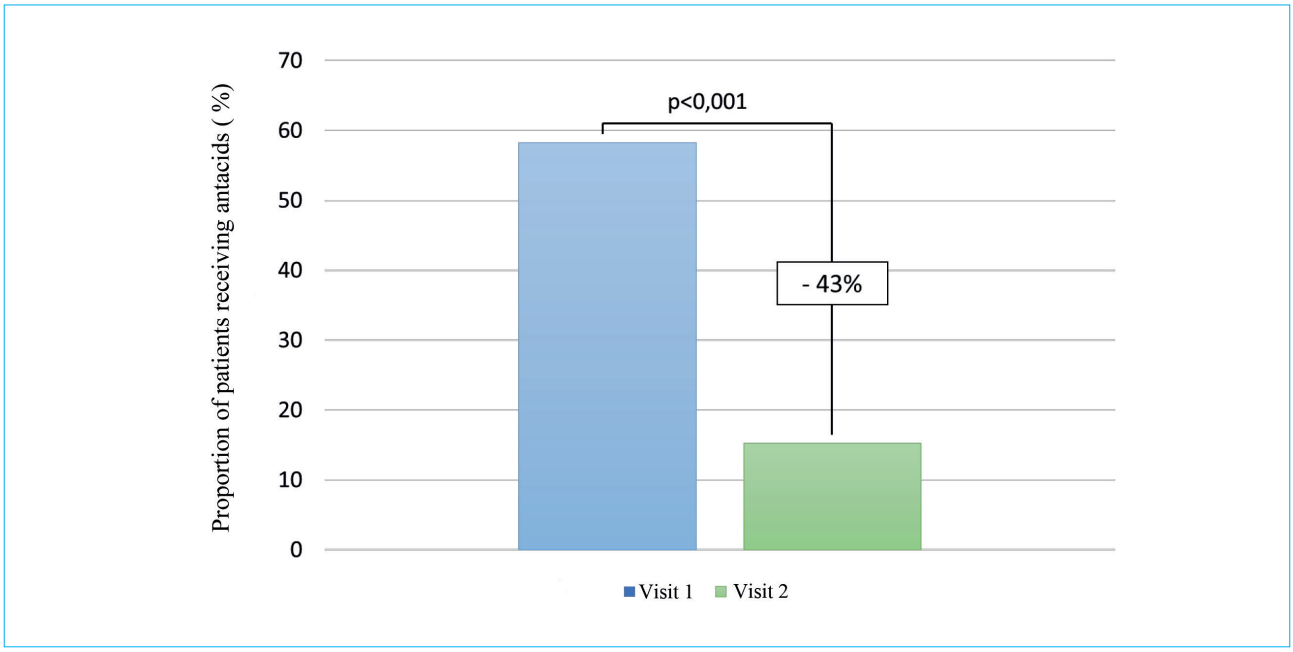

Fig. 5. Proportion of patients receiving antacids

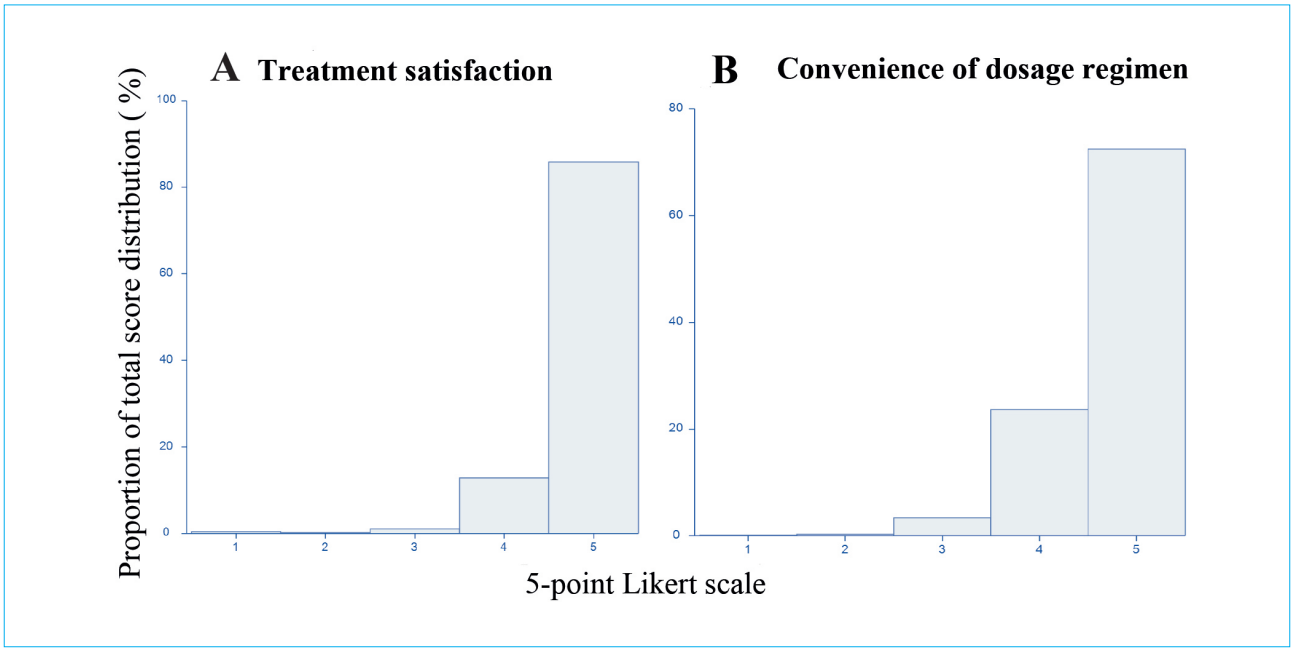

Fig. 6. Distribution of scores on a 5-point Likert scale when assessing treatment satisfaction (A) and convenience of dosage regimen (B)

Discussion

GERD is a common acid-related disorder occurring as a consequence of upper gastrointestinal dysmotility that manifests with atypical extraesophageal symptoms in about one third of patients [3, 13, 19]. Efficacy of monotherapy with PPIs in patients presenting extraesophageal symptoms of GERD remains disputable. In particular, two meta-analyses have revealed no marked benefits of PPI administration in this population [29, 30]; on the other hand, certain efficacy has been demonstrated based on results of two other meta-analyses [31, 32]. However, one should understand that limited efficacy of monotherapy with PPIs is explained, among other things, by failure to eliminate deteriorating effects of pepsin and bile, i.e., aggressive factors that play a crucial role in damaging esophagus and larynx [27, 33]. This is confirmed by data from one of the recent meta-analyses that has

revealed no significant improvement in laryngoscopic symptoms in patients with extraesophageal symptoms of GERD [32]. Pepsin affects larynx cells and intracellular compartments, such as the Golgi apparatus and lysosomes, due to their low pH levels (5.0 and 4.0, respectively) [27, 34]. Pepsin action results in cell swelling, which may be suggestive of inflammatory component both in GERD and laryngopharyngeal reflux [19, 27]. In view of the above, there is a need for developing optimal standard therapy for patients with extraesophageal symptoms of GERD [27, 35–37]. In this context, use of esophageal protectors looks quite promising.

Esophageal protectors are a novel pharmacological class presented by a bioadhesive formulation based on hyaluronic acid and chondroitin sulfate (Alfasoxx) that has been developed to protect esophageal mucosa [1, 28]. Chondroitin sulfate is known to specifically bind with bioactive molecules, for example pepsin, inhibiting it [38, 39]. Efficacy of combined therapy with Alfasoxx and PPIs, when compared to monotherapy with PPIs, has been repeatedly confirmed in clinical trials that included patients with typical variants of GERD [40–43]. This multicenter, prospective, observational study has demonstrated a significant improvement of both esophageal and extraesophageal symptoms, as well as lower need in antacids administration when adding Alfasoxx to standard therapy in patients with GERD. At the end of the study patients were extremely satisfied with the treatment, which manifested in high scores on the Likert scale. It should be pinpointed that this is the first study to assess efficacy of Alfasoxx in children and adolescents (aged 6–18 years) with extraesophageal symptoms of GERD that has demonstrated clear benefit of such therapy. In general, the obtained data are consistent with recently published results from an observational study performed by J. Chmielecka-Rutkowska et al. (2019) [44]. The study by Polish authors included more than 50 patients with laryngeal symptoms and laryngopharyngeal reflux verified by fiberoptic laryngoscopy. All patients received Alfasoxx four times a day for 2 weeks, 47 % of these patients took Alfasoxx in combination with a PPI. According to the obtained results, severity of symptoms and laryngoscopic signs of laryngopharyngeal reflux, as assessed with the help of the RSI and RFS scales, significantly reduced after Alfasoxx therapy. Patients receiving Alfasoxx in combination with a PPI noted more pronounced changes in symptom improvement [44]. Apparently, Alfasoxx creates a protective layer that coats laryngeal mucosa and prevents it from damaging (by hydrochloric acid, pepsin), thus expediting its healing and regeneration. Therefore, there is a strong need in early combined therapy with a PPI and esophageal protector Alfasoxx in patients with extraesophageal symptoms of GERD to improve treatment efficacy and prognosis in this population.

Conclusion

Hence, this multicenter, prospective, observational study has demonstrated a significant improvement of both esophageal and extraesophageal symptoms, as well as lower need in antacids administration when adding Alfasoxx to standard therapy in patients with GERD.

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