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Non-interventional Pilot Study Evaluating the Efficacy and Safety of Lysozyme-based Therapy in Patients with Non-infectious Sore Throat

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Abstract

Objective. This study aimed to evaluate the efficacy and safety of lysozyme-based oral antiseptic in the therapy of non-infectious sore throat in teachers. **Materials and Methods.** A non-interventional, prospective, pilot study was conducted with two examinations. The first was performed as part of a general medical examination. If a non-infectious sore throat was confirmed by clinical checkup and all other inclusion and non-exclusion criteria confirmed, patients were offered to be enrolled in the study. After signing the informed consent form, patients were advised to use lysozyme-based lozenges, six times a day, for a period of five days. A telephone call follow-up examination was performed within 24 hours from the therapy completion. **Results.** This was a pilot study involving 25 adult patients of both genders. Lysozyme-based lozenges showed positive effects in relieving the symptoms of non-infectious sore throat in teachers. At the same time, the lozenges showed excellent tolerability, and no side effects were reported during the study. 92% of patients confirmed they would take the same medicine again due to the same problem. **Conclusion.** The results of this "proof-of-concept" study indicated that lysozyme-based antiseptic could be effective and safe in the treatment of non-infectious sore throat in teachers and should be further evaluated as treatment option in this condition.

Key Words: Lysozyme ▪ Functional Dysphonia ▪ Professional Exposure ▪ Sore Throat.

Introduction

It is estimated that around one-third of workers in the modern world use voice as the principal tool at work. Certain vocally demanding professions such as teachers, doctors, nurses, tour guides, actors and singers are at higher risk of developing throat irritation problems (1, 2). Terms such as throat irritation, functional dysphonia due to professional exposure, and throat discomfort are used as synonyms for non-infectious sore throat (3, 4). The term "non-infectious sore throat" may sometimes be confusing and insufficiently explained, resulting in the inclusion of criteria associated with acute and chronic pharyngitis of microbial etiology in studies dealing with this issue. It has to be emphasized that non-infectious sore throat can be a result of functional dysphonia (3). The problem of functional dysphonia is recognized as an important factor influencing the everyday communication, social, and professional life of affected individuals. It can result in social isolation, increased need for sick leave, and depression (5).

In pre-clinical and clinical models, inflammation and underlying mechanisms of non-infectious sore throat were evaluated. A rat experimental model of pharyngitis induced by pyridine solution

was used to investigate the role of inflammation and immune response in non-infectious sore throat (6). In this model, microscopic changes as well as increased levels of tumor necrosis factor alpha (TNF-α), interleukin - 6 (IL-6) and expression of defensins' genes were observed. Those changes could be mitigated by application of phytochemical preparations with immunomodulatory and anti-inflammatory activities (7, 8). Non-infectious sore throat was investigated in clinical settings as well, when pharynx was exposed to cold dry air and acute response characteristic for non-infectious sore throat was provoked. It caused a feeling of pain and short-term increase of inflammatory parameters (prostaglandin E2, thromboxane B2, and substance P) in pharyngeal lavage fluid (9). In a similar manner, prolonged mouth breathing (10) and obstructive sleep apnea (11) can lead to inflammation.

Although there is no unique doctrine in the treatment, anti-inflammatory medicines and oral antiseptics are usually used along with vocal hygiene (3). Lysozyme is an enzybiotic with immunomodulatory and anti-inflammatory effects (12) that could be utilized in non-infectious sore throat treatment (13). Due to its pharmacological effects and natural origin, lysozyme is an interesting and potentially efficacious treatment of non-infectious sore throat.

The objective of this pilot non-interventional prospective study was to evaluate the results of monitoring the efficacy and safety of lysozyme-based oral antiseptic in the therapy of non-infectious sore throat in teachers.

Materials and Methods

A non-interventional pilot study to evaluate the efficacy and safety of lysozyme-based therapy in patients with non-infectious sore throat was conducted at the Institute of Occupational Medicine, Health Care Centre of Canton Sarajevo, Bosnia and Herzegovina, from July to September 2020. The primary aim was to treat non-infectious sore throat in teachers with lysozyme-based lozenges and evaluate the efficacy of therapy through collection of data using a validated questionnaire (14) for Rating Quality of Life Related to Sore Throat where the answers are rated on the Likert scale from 1 (lowest) to 5 (highest) with exception of the question "Are you able to take care about yourself completely?" where scale from 1 (highest) to 5 (lowest) was used. Secondary aims were to evaluate the safety of lysozyme-based lozenges by monitoring the frequency and types of adverse events during the therapy and to investigate the characteristics of non-infectious sore throat as a result of a secondary reaction to functional dysphonia in teachers.

Patients

The study included patients of both genders, aged 18 years and older, employed as teachers and with symptoms of non-infectious sore throat confirmed on the basis of clinical examination by medical doctor. Non-inclusion criteria were symptoms of infectious sore throat confirmed on the basis of a clinical examination by medical doctor, usage of empirical antibiotic therapy due to a previously diagnosed infectious sore throat, usage of preparations for the treatment of sore throat in the form of sprays or lozenges, malignant disease, hypersensitivity to the active substance and / or excipients of the drug, hypersensitivity to egg whites, pregnancy and lactation. Exclusion criteria were exacerbation of the underlying disease and development of serious adverse events requiring discontinuation of therapy.

Study Drug

After signing the informed consent form, patients were advised to use Lysobact® lozenges (compressed lozenges with smooth undamaged edges and 8 mm diameter containing lysozyme hydrochloride 20 mg and pyridoxine hydrochloride 10 mg as active ingredients and lactose monohydrate, tragacanth, saccharin sodium, magnesium stearate, and vanillin as excipients, producer: Bosnalijek d.d., Bosnia and Herzegovina). Six lozenges were used during the day for a period of five days, according to the valid patient information leaflet (15). It was recommended that lozenges should be allowed to slowly

melt under the tongue with an interval of at least one hour between each intake. A follow-up telephone examination was performed on the sixth day (within 24 hours after the end of therapy).

Data Collection

First examination was performed as part of a general medical examination. Figure 1 shows the monitored parameters. In Supplemental data, the test list used in the study is provided.

Ethical Statement

The study was conducted according to the criteria set by the Declaration of Helsinki of 1975, as revised in 2000, and each patient signed an informed consent before enrolment to the study.

Statistical Analysis

The descriptive statistics was performed and data were presented as absolute values and percentages or as medians and interquartile range (IQR). Wilcoxon signed rank test was used to determine differences in subjective feeling of pain, difficulty swallowing, and the posterior pharyngeal wall swelling at first and follow-up examination. $P<0.05$ was accepted as statistically significant. The statistical analysis was performed in Statistical Package for the Social Sciences (SPSS) IBM Version 26 (SPSS) (UNICOM Systems, Inc.)

Results

25 patients were included, 5 men and 20 women. Patients' baseline characteristics are presented in Table 1.

Table 1. Baseline Characteristics of Patients Involved in the Study. Data Is Presented as Absolute Numbers and Percentages

Characteristics	Total number of patients N=25; (%)
Age (Years)	
50 - 65	6 (24)
30 - 50	18 (72)
18 - 30	0 (0)
Unknown	1 (4)
Gender (Female / Male)	20 (80) / 5 (20)
Work experience (Years)	
<5	0 (0)
5 - 10	6 (24)
10 - 20	10 (40)
20 - 30	7 (28)
>30	2 (8)
Working place	
Primary School	7 (28)
High School	18 (72)

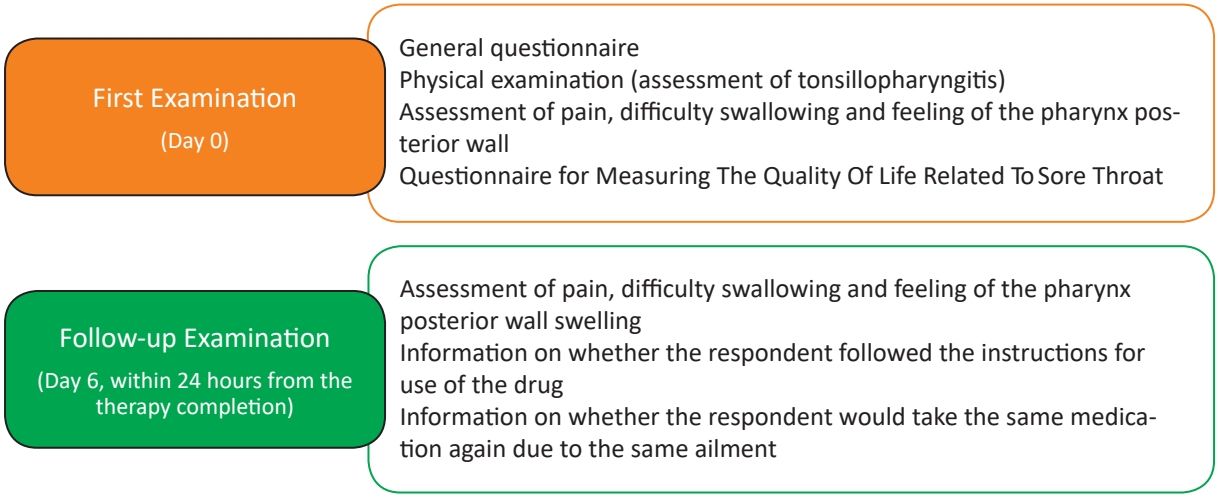

Figure 1. Study design.

First Examination Results

The first examination results were used for evaluation of the characteristics of non-infectious sore throat in teachers. The general questionnaire showed that most patients felt dry throat during the day, used some of the throat preparations, throat problems made them nervous, and throat discomfort decreased when they were silent. On the other side, a small number of patients often visited a doctor due to a sore throat or had a confirmed allergy (Figure 2). Physical examination revealed that none of the subjects had an oropharyngeal enanthema (vesicles, petechiae, exudate). Most patients had normal tonsil size (N=17), two patients had slightly enlarged, two patients had moderately enlarged, one patient had considerably enlarged, while three patients had removed tonsils. The color of the oropharyngeal mucosa was normal in 24 patients, while in one patient it was red.

The questionnaire for measuring the quality of life related to sore throat examined the impact of non-infectious sore throat in the patients through the physical, psychological, social, and environmental domains (Table 2). In the physical domain, it was observed that there was a mild to moderate sore throat, moderate effect on swallowing, little or no effect of sore throat on sleep and breathing, little effect on exhaustion and movement, and that most patients could fully take care of themselves. In the psychological domain, it has been observed that sore throat moderately deconcentrated most of the patients, while it did not make them depressed or affected their daily religious activities. In the social domain, it was noticed that for the majority of patients, sore throat moderately interfered with work, had little interference in relationships with family members and socializing with friends, and almost no interference in monitoring media content or sexual activity. In the domain of the environment, it has been found that sore throat had a small effect on colleagues at work or prevention of others from associating with patients, almost never led to financial losses and endangered personal

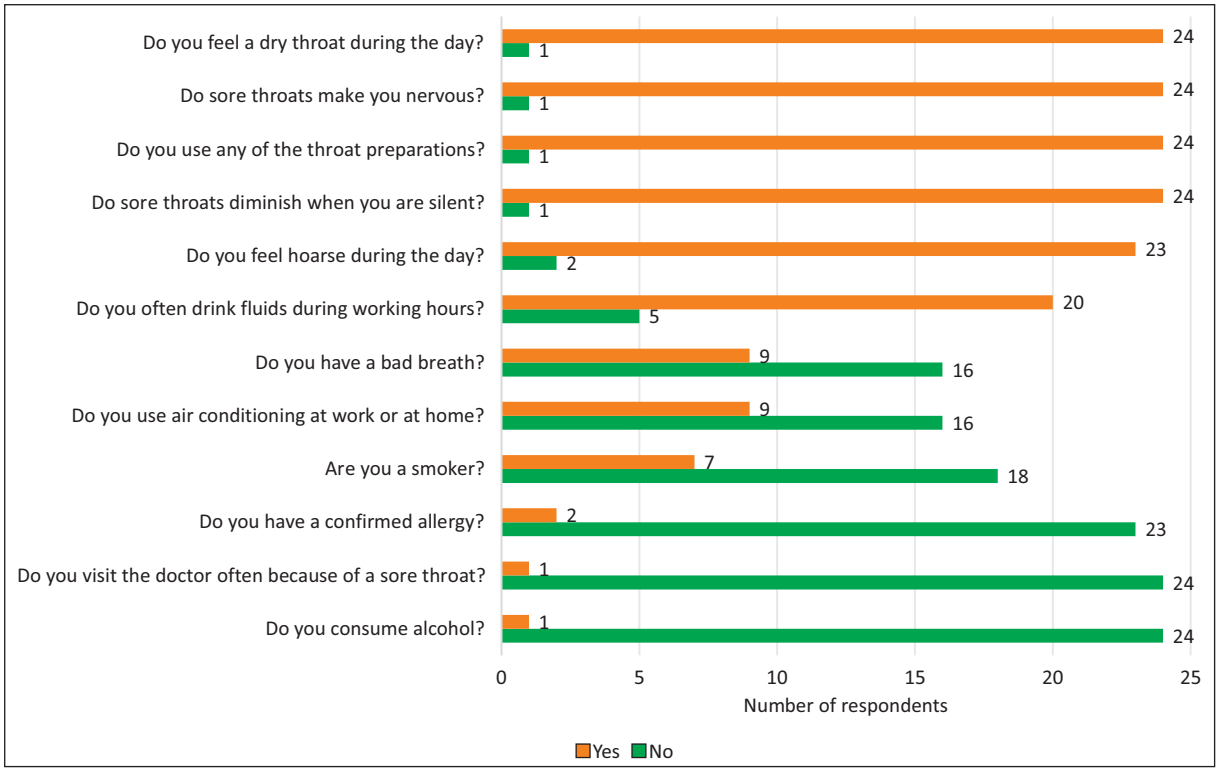

Figure 2. The general questionnaire results.

Table 2. Results of the Questionnaire for Rating Quality of Life Related to Sore Throat. The Answers Are Rated on the Likert Scale from 1 (lowest) to 5 (highest) with Exception of the Question "are You Able to Take Care about Yourself Completely?"Where Scale from 1 (highest) to 5 (lowest) Was Used

Domain	Median	IQR
Physical	2.00	1.00 - 3.00
How much your throat hurts, i.e. "burns" or "scratches"?	3	2 - 3
Does sore throat make swallowing difficult?	3	2 - 3
How much sore throat affects your sleep?	2	1 - 2
Does sore throat make breathing difficult?	2	1 - 2
Do you feel exhausted due to sore throat?	2	2 - 3
Are you able to take care about yourself completely?	1	1 - 1
Do you walk less due to the sore throat?	2	1 - 2
Psychological	1.00	1.00 - 2.50
How much sore throat affects your concentration?	2	2 - 3
Does sore throat make you depressive?	1	1 - 2
Does sore throat interfere with your daily religious activities?	1	1 - 2
Social	2.00	1.00 - 2.00
Does sore throat affect your relations with family members?	2	1 - 2
Does sore throat interfere with your work?	3	2 - 3
Does sore make following media more difficult?	1	1 - 2
Does sore throat interfere with your friendships?	2	2 - 2
Does sore throat interfere with your sexual activities?	1	1 - 2
Environment	2.00	1.00 - 2.75
Does sore throat make your colleagues at work uncomfortable?	2	1 - 2
Do you have financial losses due to the sore throat?	1	1 - 1
Does sore throat impair your personal security?	1	1 - 2
Does your sore throat prevent others to socialize with you?	2	1 - 2
Does sore throat impair your ability to withstand pollution of air in the city?	3	2 - 3
Does sore throat impair your ability to withstand heat or coldness?	2	1 - 3

IQR=Interquartile range.

safety, and moderately affected the endurance of air pollution in the city, heat or cold (Table 2). At the end of the questionnaire, the patients indicated quality of life on a scale from 0 to 100, where the median was 85 (IQR 80 - 85).

Follow-Up Examination Results

Data from the follow-up examination existed for 24 patients, while one patient did not provide answers for follow-up examination. All patients confirmed that they followed the instructions for use of the drug. Significant improvement was observed in pain, difficulty in swallowing, and feeling of the posterior pharyngeal wall swelling suggesting drug efficacy in non-infectious sore throat.

The median value of pain assessment at the first examination was 3 (IQR 1 - 4) compared to the follow-up examination where it was 0 (IQR 0 - 1), with a significant decrease after application of lysozyme-based therapy (P<0.001) (Figure 3). Six patients (24%) reported no pain at the first examination. At the follow-up examination none of the patients reported a worsening of the pain. Out of 18 patients who reported pain at the first examination, data for one patient was missing while all other patients reported a reduction in pain at follow-up. Nine patients who reported the presence of pain at the first examination, at the follow-up reported that the pain no longer existed.

The median value of the swallowing difficulty at the first examination was 3 (IQR 1 - 4) compared to the follow-up examination where it was 0 (IQR 0 - 1), with a significant decrease after applied therapy (P<0.001) (Figure 4). Four patients (16%) reported that there was no difficulty in swallowing at the first examination. Out of 21 patients who reported difficulty in swallowing at the first examination, at follow-up data was missing for one patient, none reported a deterioration in symptoms, one patient reported no improvement, while the other 19 reported an improvement. Ten patients who reported having difficulty swallowing at the first examination reported that difficulty no longer existed at the follow-up.

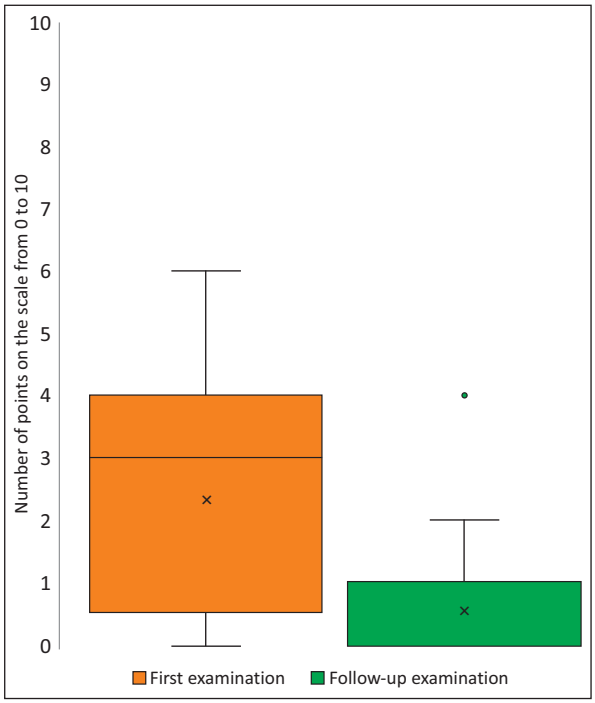

Figure 3. Assessment of pain at the first and follow-up examination. The median value was significantly decreased at the follow-up compared to the first examination (P<0.001). The middle line in the box represents median, the bottom line first quartile and the top line third quartile. The x in the box represents the mean and the whiskers extend to the minimum and maximum values, if no outliers are present or the first quartile minus 1.5 × interquartile range (IQR) and the third quartile plus 1.5 × IQR, if outliers are present. Outliers are represented by dots below or above whiskers.

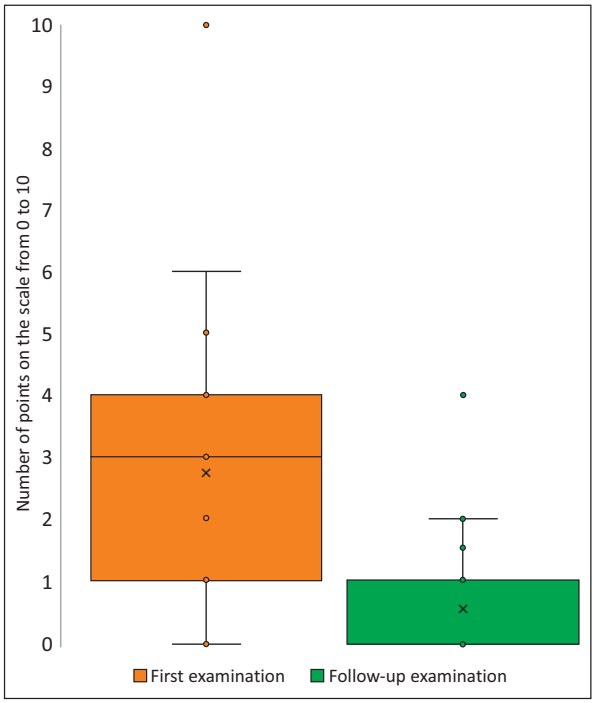

Figure 4. Assessment of swallowing difficulty at the first and follow-up examination. The median value was significantly decreased at the follow-up compared to the first examination (P<0.001). The middle line in the box represents median, the bottom line first quartile and the top line third quartile. The x in the box represents the mean and the whiskers extend to the minimum and maximum values, if no outliers are present or the first quartile minus 1.5 × interquartile range (IQR) and the third quartile plus 1.5 × IQR, if outliers are present. Outliers are represented by dots below or above whiskers.

The median value of the pharynx posterior wall swelling feeling at the first examination was 2 (IQR 1 - 4) compared to the follow-up examination where it was 0 (IQR 0 - 1), with a significant decrease after applied therapy (P<0.001) (Figure 5). Six patients (24%) reported at the first examination that there was no subjective feeling of swelling of the pharynx posterior wall. Out of 19 patients who reported swelling of the pharynx posterior wall at the first examination, at follow-up for one patient data was missing, none reported a worsening of the symptoms, two patients reported no improvement, while the other 16 reported improvement. Most patients reported an improvement of three points on a scale between 0 and 10. Ten patients who reported the presence of the pharynx posterior wall swelling at the first examination, reported at the follow-up that the feeling of swelling no longer existed.

22 patients (92%) at the follow-up examination confirmed that they would take the same medicine again due to the same problem. No drug adverse effects were reported in this study suggesting good safety of evaluated drug.

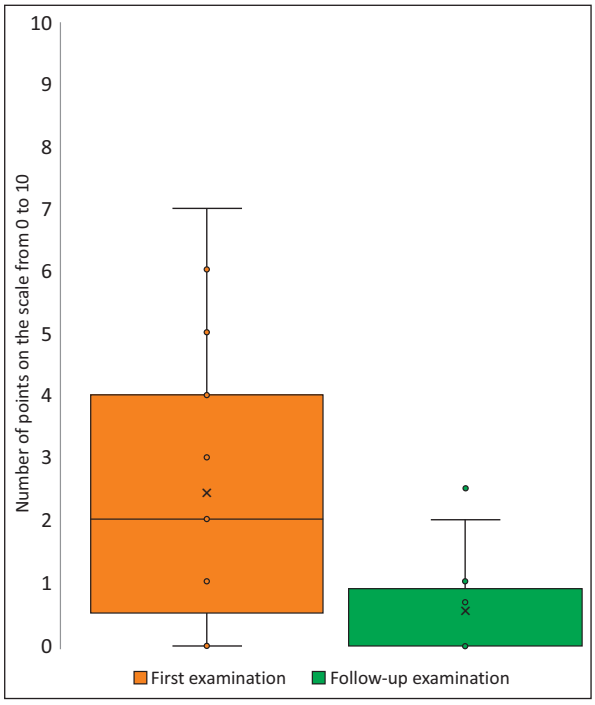

Figure 5. Assessment of the feeling of the pharynx posterior wall swelling at the first and follow-up examination. The median value was significantly decreased at the follow-up compared to the first examination (P<0.001). The middle line in the box represents median, the bottom line first quartile and the top line third quartile. The x in the box represents the mean and the whiskers extend to the minimum and maximum values, if no outliers are present or the first quartile minus 1.5 × interquartile range (IQR) and the third quartile plus 1.5 × IQR, if outliers are present. Outliers are represented by dots below or above whiskers.

Discussion

The results of this non-interventional pilot study indicated that lysozyme-based lozenges could have positive effects in relieving the symptoms of non-infectious sore throat in teachers. In the same time, the drug was found to be safe as there were no adverse effects reported in this study. This is the first study evaluating effects of lysozyme based medicines on non-infectious sore throat, but already known mechanism of action of this enzybiotic indicated that it could be beneficial for resolving non-infectious sore throat (12).

A significant improvement was observed in pain, difficulty swallowing, and subjective feeling of the posterior pharyngeal wall swelling after application of lysozyme-based therapy. 92% of the patients confirmed that they would take lysozyme-based lozenges again to treat the same problem. Beneficial effects of applied lozenges could be due to active substances lysozyme or pyridoxine but also due to effects of sucking lozenges.

Lysozyme's mechanisms of activity can be utilized to overcome inflammation in non-infectious sore throat. Lysozyme used in the pharmaceutical industry for the production of oral antiseptics and other lysozyme-based products, is derived from hen egg-white (16). This enzyme suppresses TNF-α and IL-6 in mouse macrophages (17), the main players in non-infectious sore throat inflammation (9, 10, 18, 19). Anti TNF-α activity of lysozyme was shown in human monocyte cells (20). Another active component of a drug used in this study, pyridoxine, is efficacious in treatment of diseases of oral cavity, gingivitis and glossitis. Pyridoxine has significant role in treatment of oral aphthae, pain and burning sensations in mouth (21). Lysozyme and pyridoxine combination is recommended for local treatment of painful aphthae as natural healing agent (22). In addition to active components activity, sucking lozenge could increase the salivary flow rate and lead to relieved symptoms in our patients. According to Tenovuo et al., a significant increase in salivary flow rate was observed immediately (2 - 4 min) after sucking the lozenge. Also, after the daily use of lozenge for one month the baseline flow rate was significantly elevated (23).

In addition to the proof-of-concept evaluation of lysozyme-based products in the treatment of non-infectious sore throat, this study investigated the characteristics of non-infectious sore throat in teachers, a high-risk profession for voice disorder as an occupational disease (24, 25). The most commonly studied group of professional voice users are teachers (1). In a study conducted in Brazil, non-infectious sore throat was reported by 63% of teachers (N=1651) and 36% of non-teachers (N=1614) (26). In a study conducted in Sweden, voice disorders were reported by 19.3% of teaching professionals (N=1173) (27). Behlau et al. reported

that the lifetime prevalence of non-infectious sore throat in teachers increases in the age group 30–39 years and persist across increasing ages. Also they found that women had higher prevalence of non-infectious sore throat across all ages (26). Non-infectious sore throat is usually manifested as vocal fatigue, hoarseness, throat pain or discomfort, weak voice, dryness, and lower pitch. Prevalence of symptoms in teachers after a long periods of voice usage in the classroom are vocal fatigue (52%), sore or dry throat (34%), vocal strain (29%), neck muscle tension (19%) and difficulty in projecting the voice (14%) (28).

We showed that non-infectious sore throat is a condition with moderate symptoms (medians for sore throat intensity and difficulty in swallowing were 3 on a scale between 1 and 5, most patients felt dry throat during the day, had normal tonsil size, none of the patients had an oropharyngeal enanthema and oropharyngeal mucosa was normal in 96% of patients). Non-infectious sore throat is generally less intensive when compared to infectious etiology (3, 4) and can be accompanied with pharyngitis as an isolated finding (10). Still, this condition can influence the quality of life in affected individuals (24) as we also found in our study (the median value of sore throat interference with work was 3 on a scale between 1 and 5, IQR 2 - 3). In a study with 1326 participants, 4.3% of them said that the voice disorder disabled them in their working tasks, and 7.2% were absent from work due to voice problems (25). In our study, the patients indicated the quality of life on a scale from 0 to 100, with the median 85 (IQR 80 - 85).

Risk factors for sore throat can be divided into different domains (physical, psychological, social, and environmental). In our study, physical, social, and environmental domains had medians of 2 on Likert scale from 1 (lowest) to 5 (highest) with exception of the question "Are you able to take care about yourself completely?" where scale from 1 (highest) to 5 (lowest) was used. Physical domain had the third quartile value 3, the highest among all domains (Table 2). Similarly, Kooijman et al. found that the highest risk factors for voice problems in teachers are within the physical and psycho-emotional domains. They found that appropriate voice training is of importance during teachers' education (29).

The most important risk factors for non-infectious sore throat development are female gender (24, 25, 29-32), air pollution (4), smoking, consuming alcoholic beverages (4, 22), and existing allergies (24, 32). We found that non-infectious sore throat impairs teachers' ability to withstand air pollution in the city. Additionally, a much higher proportion of patients in our study were women (80%). Some of the risk factors are diminished in teachers as a specific population. For instance, they are less likely to smoke or consume alcoholic beverages, compared to the general population (4, 24). In our study, only 1 in 25 patients (4%) consumed alcohol and 7 in 25 patients smoked (28%). In addition, only 2 in 25 patients (8%) had confirmed allergies. Despite the impact of non-infectious sore throat on life quality, there is a small number of patients looking for medical help due to this condition (4). Roy et al. found that 14.3% of teachers visited a doctor or speech-language pathologist for voice disorder (24), and in our study only 1 in 25 patients (4%) visited a doctor often due to the sore throat.

Limitation of Study

This was a pilot study involving 25 patients and only teachers were included. Only five patients (20%) were of male gender. Also, the study did not include control group, randomization and blinding. This was a "proof-of-concept" study and should be confirmed in controlled, blinded, randomized clinical trial on larger number of patients and in case of confirmation of drug efficacy and safety this drug should be considered as a treatment option for non-infectious sore throat.

Conclusion

This was a "proof-of-concept" study suggesting that lysozyme-based drugs in the form of lozenges might have positive effects in relieving the symptoms of non-infectious sore throat in teachers. At

the same time, the studied lozenges showed excellent tolerability and safety.

What Is Already Known on This Topic:

Non-infectious sore throat is a condition with significant effects on quality of life in persons using voice professionally, including teachers. Still, this condition is poorly recognized and therapeutic options are scarce. As inflammation is the underlying mechanism, compounds with anti-inflammatory and immunomodulatory effects are of great interest to be evaluated as therapeutics for non-infectious sore throat.

What This Study Adds:

This pilot study suggested positive effects of lysozyme based medication in treatment of non-infectious sore throat.

Authors' Contributions: Conception and design: SK, DŽH, MM, AŠ, JDŽJ, ATA, AS, AD, ZS and UG; Acquisition, analysis and interpretation of data: SK, DŽH and UG; Drafting the article: SK, MM, JDŽJ, ATA and UG; Revising it critically for important intellectual content: AŠ; Approved final version of the manuscript: SK, DŽH, MM, AŠ, JDŽJ, ATA, AS, AD, ZS and UG.

Conflict of Interest: Meliha Mehić, MD; Aziz Šukalo, MD; Jasna Džananović Jaganjac, PhD; Amna Tanović, MD; Una Glamočlija, PhD; disclose the following relationships – employees of Bosnalijek d.d., a pharmaceutical company producing lysozyme-based products. Bosnalijek d.d. had a role in the design of the study; in the collection, analyses, and interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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Appendix

Translated test list used for the study
Name of the study:
Non-interventional Pilot Study Evaluating the Efficacy and Safety of Lysozyme-based Therapy in Patients with Non-infectious Sore Throat

Patients' initials:

Number of patient:

GENERAL QUESTIONNAIRE

Gender: Male Female

Age: 18 - 30 30 - 50 50 - 65

Length of service:
☐ < 5 years
☐ 5 do 10 years
☐ 10 do 20 years
☐ 20 do 30 years
☐ > 30 years

Working place: ☐ Elementary school ☐ High school ☐ Music school

How often do you use your voice without a break during the day?

☐ Less than 30 minutes ☐ 30 - 60 minutes ☐ More than 60 minutes

Do you smoke? YES NO

Do you consume alcohol? YES NO

If the answer is YES, state the average number of alcoholic beverages during:

Week ____ Month ____ Year ____

Do you use air conditioning at work or at home? YES NO

Do you have a confirmed allergy? YES NO

If the answer is YES, specify the type of allergy _____

Do you feel hoarse during the day? YES NO

If the answer is YES, state how often you feel hoarse _____

Do you feel a dry throat during the day? YES NO

If the answer is YES, state how often you feel a sore throat _____

Do you drink fluids often during working hours? YES NO

If the answer is YES, state how much fluid you drink during the day (L) _____

Do you have a bad breath? YES NO

Does a sore throat make you nervous? YES NO

Do sore throat decrease when you keep quiet? YES NO

Do you visit the doctor often because of a sore throat? YES NO

If the answer is YES, how often have you visited a doctor in the last year for a sore throat? _____

Do you use any of the preparations for throat? YES NO

If the answer is YES, specify the type of preparation: _____

FIRST EXAMINATION

PHYSICAL EXAMINATION (assessment of tonsillopharyngitis)

Oropharyngeal mucosa color

Normal/ Pink or slightly red ☐ Red ☐ Very red ☐

The size of the tonsils

Normal/ Not increased ☐ Slightly increased ☐ Moderately increased ☐ Very increased ☐

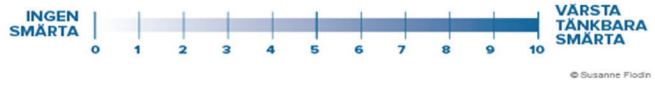
Oropharyngeal enanthema (vesicles, petechiae, exudate)

Not present ☐ Few ☐ Many ☐ Very much ☐

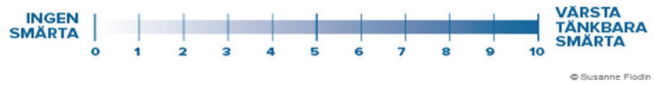
ASSESSMENT OF PAIN, DIFFICULTY IN SWALLOWING AND SUBJECTIVE FEELING OF THE POSTERIOR PHARYNGEAL WALL SWELLING

Instructions: Mark the strength/intensity with a cross

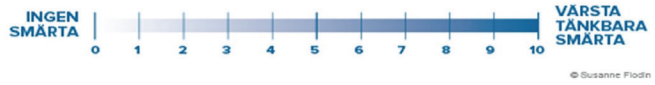
Pain



Difficulty swallowing



Subjective feeling of swelling of the posterior wall of the pharynx

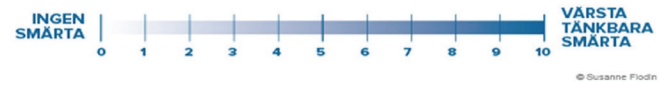


** During the first examination, the Questionnaire for Measuring the Quality of Life Related to Sore Throat is also filled in (attached to the test list)*

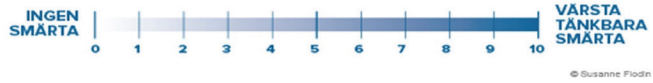
FOLLOW-UP EXAMINATION

Instructions: Mark the strength/intensity with a cross

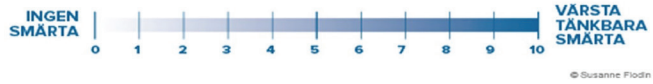
Pain



Difficulty swallowing



Subjective feeling of swelling of the posterior wall of the pharynx



Have you followed the instructions for use of the medicine? YES NO
Would you take same medicine again because of the same ailment? YES NO