European Review for Medical and Pharmacological Sciences 2021; 25: 999-1005

Effect of omeprazole on symptoms of gastroesophageal reflux disease in children with cystic fibrosis. A randomized, double-blind, placebo-controlled trial

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Abstract. – OBJECTIVE: The incidence of gastroesophageal reflux disease (GERD) is higher in patients with cystic fibrosis (CF) than in the general population. While the relationship between GERD and its typical symptom, heartburn, is beyond doubt, its effect on cough or abdominal pain is unclear. In CF patients, in particular, it is often difficult to confirm the causal relationship between GERD and these symptoms. The aim of this trial was to evaluate the effect of omeprazole treatment of GERD on abdominal pain and cough, in children with CF.

PATIENTS AND METHODS: This was a multicentre, randomized, double-blind, placebo-controlled trial. All children aged 4-18 years underwent 24-hour multichannel intraluminal pH-impedance monitoring. The patients with diagnosed GERD were randomly assigned to receive omeprazole (20 mg twice daily for 12 weeks) or placebo. The severity of symptoms was assessed on visual analog scale.

RESULTS: 22 consecutive patients (median age 11.02± 3,67, range 6.4-17.0) were enrolled. A statistically significant reduction in abdominal pain and typical GERD symptoms, but not cough, was observed in both omeprazole (N=12) and placebo (N=10) groups. However, there were no statistically significant differences between the groups in the degree of reduction. We did not observe any differences between the groups in terms of adverse reactions.

CONCLUSIONS: Treatment of GERD in children with CF seems not to have a stronger effect than a placebo on the severity of cough and abdominal pain. Considering this, as well as the previously raised concerns about the impact of chronic proton pump inhibitor treatment on the course of CF, perhaps one should be more careful in intensively treating suspected atypical GERD symptoms in patients with CF.

Key Words:
Cystic fibrosis, Gastroesophageal reflux disease, Proton pump inhibitors, Cough, Abdominal pain.

Abbreviations
CF = cystic fibrosis; GERD = gastroesophageal reflux disease; ESPGHAN = European Society of Pediatric Gastroenterology, Hepatology and Nutrition; PPI = proton pump inhibitor; 24 hr MII/pH = 24-hour multichannel intraluminal impedance with pH-metry; GER = gastroesophageal reflux episodes; AGER = acid gastroesophageal reflux episodes; NAGER = non-acid gastroesophageal reflux episodes; RI = reflux index; RTI = respiratory tract infection.

Introduction

Cystic fibrosis (CF) is the most common disease caused by a single gene mutation in the Caucasian population. Its prevalence is approximately 0.737/10,000 in the European Union[1]. Mutation of the *CFTR* gene, which encodes cystic fibrosis transmembrane conductance regulator, leads to a disruption of transmembrane transport of Cl^- ions and an increase in Na^+ and water absorption. It results in abnormally viscid exocrine gland secretions.

The spectrum of CF symptoms is very broad and extends beyond the respiratory system. The symptoms depend on the mutation in both the *CFTR* gene and the so-called "modifier genes"[2]. It

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is currently estimated that several dozen CF complications are related to the gastrointestinal tract[3]. The pathomechanism of some of them, like pancreatic exocrine insufficiency, is directly related to the *CFTR* gene mutation, while the etiopathogenesis of others is more complex. Among the latter is gastroesophageal reflux disease (GERD). Its incidence is higher in patients with CF than in the general population, and it is estimated to occur in up to 66% of children with CF[4].

GERD, *via* microaspiration and reflex bronchospasm due to irritation of the esophageal mucosa, can negatively affect the course of pulmonary disease in CF[5]. It also has a negative impact on the nutritional status in patients with CF[6].

Typical symptoms of GERD are heartburn and regurgitation. Their presence allows treatment to start without any additional diagnostic tests being performed. Other, much less specific, symptoms of GERD are abdominal pain and cough. According to European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommendations[7], empirical proton pump inhibitor (PPI) therapy should not be used for atypical GERD symptoms. In CF patients, in particular, it is often difficult to confirm the causal relationship between GERD and these symptoms. Most often, the diagnosis of GERD is made only on the basis of confirmation of excessive acid esophageal exposure by 24-hour pH-metry or 24-hour multichannel intraluminal impedance with pH-metry (24hr MII/pH).

The main group of medications used in GERD treatment are PPIs. Although their safety profile is encouraging, the long-term use of PPIs is suggested to have potential adverse effects. Those include the increase of the number of respiratory infections or CF exacerbations[8,9].

Given the diagnostic difficulties in children with extra-esophageal GERD symptoms and the potential complications of chronic use of PPI, it is important to determine the effect of GERD treatment on the severity of cough and abdominal pain in children with CF. No such study has yet been published.

Patients and Methods

Study Design

This randomized, double-blind, placebo-controlled trial was conducted in the Department of Pediatric Gastroenterology and Nutrition, Medical University of Warsaw, and the Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, and the Cystic Fibrosis Center, Institute of Mother and Child. The study protocol was approved by the Ethics Committee of Warsaw Medical University in Poland. Informed written consent was obtained from parents or legal guardians after they were fully informed about the aims of the study.

Participants

Eligible participants were children between 4 and 18 years old diagnosed with CF according to established criteria[10]. Exclusion criteria included disorders other than CF that might affect gastrointestinal motility. Children who had taken medications that might impact esophageal motility and/or stimulate/inhibit the secretion of gastric contents in the 2 weeks prior were also excluded. Those taking these medications who wished to take part in the study could stop the medications mentioned above for 14 days.

Interventions

Participants were randomly assigned to receive oral omeprazole at a twice-daily dose of 20 mg or placebo for 12 weeks. Both the active product and the placebo were packaged in identical, opaque capsules that tasted the same. All participants were instructed to take their study medication 30 min before breakfast and 30 min before dinner.

Randomization and Masking

A computer-generated randomization list was used to allocate participants with a block size of four. The list was prepared by someone who was not involved directly in the trial. All investigators were blinded to the block size until all the data were analyzed. If all inclusion criteria were met by the participant, the enrolling physician contacted by phone a person not directly involved in the trial, who assigned the patient to the group according to the code. All of the investigators and caregivers, as well as the statistician, were blinded to the intervention until the completion of the study and the analysis of the data.

Procedures

Participant demographic data and medical comorbidities were recorded at screening. After informed consent was obtained, all patients underwent 24hr MII/pH. Two types of probes were used: ZPN-BS-46 M for children younger than 10 years and ZAN-BS-01 M for older children (Sandhill Scientific, Denver, CO, USA). The position of the probe was controlled radiologically to confirm that the pH sensor was located at the level of the 3rd vertebrae above the diaphragm. The data were an-

alyzed automatically using BioView software (ver. 5.4.3, Sandhill Scientific, Denver, CO, USA) and verified manually. To ensure consistency, the analysis was performed by one researcher (MD). Gastroesophageal reflux episodes (GER) were classified based on commonly accepted criteria as acid GER (AGER), non-acid GER (NAGER), and proximal GER. The percentage of time with the esophageal pH below 4.0 – called the reflux index (RI) – and the volume of the refluxate were calculated. GERD was diagnosed if the RI exceeded 4.5%.

Subjects were asked to assess the intensity of cough, abdominal pain, and typical GERD symptoms (heartburn and/or regurgitation) on a visual analog scale (1–10 points) in the past 7 days before entering the study. After 12 weeks of treatment, all patients again underwent 24hr MII/pH.

Outcome Measures

The primary outcome measures were the degree of reduction in the severity of cough and abdominal pain. The secondary outcome measures were the degree of reduction in the severity of typical GERD symptoms, as well as reduction of RI and number of AGER, NAGER, and proximal GER episodes. Any adverse effects of the treatment were also recorded.

Sample Size

Due to the pilot character of the trial, no formal sample size calculation was performed. It is suggested that 20-30 participants per treatment group should provide sufficient data to assess the feasibility of a pilot trial, investigate the distribution of outcome measures, and estimate with adequate precision standardized differences of key study parameters[11].

Statistical Analysis

Data were analyzed on an intention-to-treat basis. Statistical analysis was performed using Statistica software (version 13.1, Dell Inc., Round Rock, TX, USA). Data are presented as median (25^{th}-75^{th} percentile) unless otherwise stated. To compare changes in parameters between groups, Mann-Whitney test, analysis of variance with replication, and contrast analysis were performed. Statistical significance was accepted if $p < 0.05$.

Results

A total of 37 patients were screened. Inclusion criteria were met by 22 patients, who were randomized to the omeprazole group (12 patients) or the placebo group (10 patients). No statistically significant differences were found between the groups in terms of demographic characteristics, clinical and 24hr MII/pH parameters, and pH-impedance (Table I and II).

Table I. Baseline characteristics of the study groups.

	Omeprazole n=10	Placebo n=12	*p*
Age [mean, years]	8.08	10.085	0.64
Symptom severity [median, IQR]			
Cough	3 (2-4)	2.25 (0-4)	0.45
Abdominal pain	4.25 (2-6)	4.25 (3.5-5.25)	0.84
Typical GERD symptoms	1 (0-3)	0 (0-1.75)	0.31
Reflux index [%]	5.3 (4.9-9.1)	5.4 (4.8-7.0)	0.64
Number of GER types			
AGER	37 (21-61)	27 (13.5-37.5)	0.26
NAGER	11 (3-11)	6.5 (3.5-8.5)	0.28
Proximal	18.5 (15-33)	15 (8.5-22)	0.19
Total	44 (37-64)	36 (17.5-47)	0.13
Exocrine pancreatic insufficiency	8	10	0.53
Nasal polyps	3	3	0.12
CFRD	1	1	0.20
	Detection of SARS-CoV-2		

The severity of symptoms was determined using visual analog scale (1-10 points). IQR – interquartile range, GERD – gastroesophageal reflux disease, GER – gastroesophageal reflux episodes, AGER – acid gastroesophageal reflux episodes, NAGER – non-acid gastroesophageal reflux episodes, CFRD – cystic fibrosis-related diabetes. Data were compared with the Mann-Whitney test.

Primary and Secondary Outcomes

After 12 weeks of treatment, a statistically significant reduction in the severity of abdominal pain and typical GERD symptoms, but not cough, was observed in both groups. However, there were no statistically significant differences in the degree of reduction between the omeprazole and placebo groups (Tables III and IV).

There was also a reduction in the value of some 24 hr MII/pH parameters: RI, AGERs, and proximal GERs in both groups. Again, however, there were no statistically significant differences between the groups. The number of total GER episodes, and especially NAGER episodes, did not significantly decreased after the intervention. For details see Tables III and IV. We did not observe differences between the groups in terms of adverse reactions. One patient in each group experienced a pulmonary exacerbation of CF not requiring hospitalization.

Discussion

The frequency of GERD in children with CF is higher than in the general population. While the relationship between GERD and its typical symptom, heartburn, is beyond doubt, its effect on cough or abdominal pain is unclear. Our study was the first to evaluate the effect of PPI treatment of GERD confirmed by 24hr MII/pH on clinical symptoms, and cough, in children with CF. The main conclusion from our study was that there was no statistically significant difference in the reduction of cough and abdominal pain between the omeprazole and placebo groups.

Table II. Characteristic of genotype of cystic fibrosis in study population.

CF genotype	Number of patients [N (%)]
CF genotype	Number of patients [N (%)]
F508del/F508del	9 (40.9%)
F508del/other	7 (31.8%)
other/other	3 (13.6%)
unknown/unknown	3 (13.6%)

CF – cystic fibrosis

Cough is the most common symptom of CF. It is most often associated with exacerbation of lung disease. Fathi et al[12], however, distinguished two clinical patterns of chronic cough in CF: productive, associated with exacerbation of lung disease, and dry, associated with throat/larynx irritation that may result from GERD. In our study, we did not find any statistically significant reduction in cough severity after treatment, regardless of the type of intervention. There are a number of possible reasons for this. First, the treatment may have not led to the resolution of GERD. Indeed, in 50% of patients in both groups after the intervention, RI still exceeded the assumed limit value (data not shown). However, when comparative analysis was performed in only the subgroup of patients in whom GERD resolved, the results remained the same. Secondly, omeprazole only affects the pH of the refluxate. Our previous observations[13], as well as those conducted by other research teams[4], showed that 24.1%–37.0% of GER episodes in patients with CF are weakly acidic. Therefore, microaspiration of gastric contents into the respiratory tract or stimulation of the esophago-bronchial reflex may still occur. Fundoplication

Table III. Changes in outcome measures before and after intervention.

	Before intervention	After intervention	*p*
Symptom severity [median]			
Cough	3	2.75	0.3
Abdominal pain	4.25	2.5	0.003
Typical GERD symptoms	0	0	0.01
Reflux index [%]	5.3	3.55	0.002
Number of GER types [median]			
AGER	30.5	23	0.04
NAGER	7.0	4.5	0.3
Proximal	16	10.5	0.004
Total	41	28	0.07

The severity of symptoms was determined using visual analog scale (1-10 points); GERD – gastroesophageal reflux disease, GER – gastroesophageal reflux episodes, AGER – acid gastroesophageal reflux episodes, NAGER – non-acid gastroesophageal reflux episodes; Data were compared with the Mann–Whitney test.

Table IV. Impact of time and type of intervention on primary and secondary outcome measures.

	Time *p*	Time and intervention *p*	Contrast analysis *p*
Symptom severity [median]			
Cough	3	2.75	0.3
Abdominal pain	4.25	2.5	0.003
Typical GERD symptoms	0	0	0.01
Reflux index [%]	5.3	3.55	0.002
Number of GER types [median]			
AGER	30.5	23	0.04
NAGER	7.0	4.5	0.3
Proximal	16	10.5	0.004
Total	41	28	0.07

GERD – gastroesophageal reflux disease, GER – gastroesophageal reflux episodes, AGER – acid gastroesophageal reflux episodes, NAGER – non-acid gastroesophageal reflux episodes. Analysis of variance with repeated measurements with contrast analysis.

is a radical surgery performed to reduce the number of GER episodes, regardless of their pH. Fathi et al[12] reported its effects in 6 adult patients with CF and GERD resistant to pharmacological treatment. After the procedure, a reduction in cough severity and in the number of CF exacerbations was found. The effects of both fundoplication[14,15] and PPI[9,16-18] on lung function and risk of exacerbation have been the subject of many other studies, but the results are conflicting. Since our study was the first to assess the effect of GERD treatment on the severity of cough in CF, we cannot compare our observations to those of other studies.

The second-most common clinical symptom present in our patients was abdominal pain. We found that after 12 weeks, its intensity statistically significantly decreased in both groups. However, there were no differences between the two groups. This may be due to two factors. First of all, the spectrum of etiological factors responsible for abdominal pain in CF is very wide[19]. Some of these pathologies, such as constipation and functional gastrointestinal disorders, may change in intensity over time without any treatment. Second, over 70% of the patients in the population we analyzed, had pancreatic exocrine insufficiency. It is suggested that by increasing the pH in the small intestine, PPI improves the bioavailability of bile acids, thus improving fat absorption[12,21]. This could reduce the severity of gastrointestinal symptoms. However, evidence for this mechanism is very poor. Robinson et al[22] noted that, among 22 children with CF receiving pancreatic enzyme replacement therapy, the addition of misoprostol resulted in a reduction in the severity of chronic abdominal pain in 6 of them. On the other hand, Dimango et al[17] did not find that esomeprazole had an advantage over placebo in reducing the severity of gastrointestinal symptoms in CF, as assessed using the Gastroesophageal Symptom Assessment Score.

Surprisingly, we found no differences between omeprazole and placebo in reducing the severity of heartburn and/or regurgitation. The effectiveness of PPI in the treatment of typical GERD symptoms in children has been previously demonstrated[23]. The most likely explanation of our results is the small study group – only 9 patients (40.9%) reported heartburn or regurgitation.

In our study, we found a higher number of AGER than NAGER episodes (79.7% *vs.* 20.3%). In other studies, the ratio was similar (62.7% *vs.* 37.3% and 65.2% *vs.* 32.8%)[4,24]. It should be noted, however, that in these studies, they analyzed the entire study population of children with CF. In our study we focused on a subgroup of those with abnormal 24hr MII/pH recording. Thus, it could be suggested that GERD in children with CF is characterized mainly by an increased number of AGER episodes. On the other hand, Hauser et al[25] had different observations. They found no differences in the percentage of different types of GER in children with normal and abnormal 24hr MII/pH recordings. These observations therefore require further research. In our study, both interventions caused the reduction of RI and AGER. Similar conclusions can be drawn from the study by Brodzicki et al[26]. However, once again, the type of intervention was statistically non-significant. In addition, the total number of GER and NAGER episodes did not change significantly. This may suggest that the GERD treatment changes of the character of GER (pH) rather than its number.

During the 12 weeks of treatment, in each group, there was one case of respiratory tract in-

fection (RTI) requiring oral antibiotic treatment on an outpatient basis. Of all the side effects attributed to PPI treatment, RTIs are the most important for CF patients. Literature data on this subject are contradictory. On one hand, an increase in the number of upper and lower RTIs was observed in children with poorly controlled asthma treated with lansoprazole for 24 weeks[8]. On the other hand, the conclusions of the meta-analysis of studies conducted in adults are contradictory; there was no significant association between PPI use and risk of RTI[27,28]. The lack of differences in the number of RTIs between the groups in our study does not seem to result from the relatively short observation time (12 weeks). Summary of systematic reviews indicated that the relationship between pneumonia and PPI is strongest in the first 7-30 days of treatment[29]. Naito et al[30] reported an impaired gut microbiota composition and function after only 28 days of lansoprazole treatment. McCrory et al[31] analyzed the side effects of chronic (at least 6 months) PPI use by patients with CF and found that the percentage of patients who experienced at least one exacerbation of pulmonary disease was significantly higher in the PPI group (59.6% *vs.* 24.5%, $p < 0.001$). It should be noted, however, that this was a retrospective analysis.

Our study has some limitations. First of all, the study population was relatively small. Second, the criteria adopted for the diagnosis of GERD (RI > 4.5%) may also raise doubts. Recent ESPGHAN guidelines for GERD in children do not point to any specific RI that enables the diagnosis of GERD[7]. Ideally, the time relationship between symptoms and GER would be confirmed. In the case of heartburn, this is relatively easy. However, in the case of chronic symptoms like cough or abdominal pain, it is difficult or almost impossible. In addition, due to age-related lack of cooperation, we were unable to perform spirometry before and after treatment. Despite all of these limitations, this is the first study that explored the effectiveness of PPI treatment on the important symptoms of cough or abdominal pain in children with CF in an objective way (randomized controlled trial). We believe that the results of our study increase the information on the real impact of symptoms of GERD in patients with CF.

Conclusions

The results of our study suggest that pharmacological (PPI) treatment of GERD in children with CF seems not to have a stronger effect than a placebo on the severity of cough and abdominal pain. Considering this, as well as the concerns about the impact of chronic PPI treatment on the course of CF, perhaps one should be more careful in intensively treating suspected atypical GERD symptoms with PPI in patients with CF. These observations require confirmation in clinical trials involving a larger group of patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Declaration of funding interests

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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