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MODERN APPROACHES TO THE TREATMENT OF PATIENTS WITH FUNCTIONAL CONSTIPATION

Summary

Objective is to study the efficacy and tolerability of the LACTOFOR® complex (Ananta Medicare) in outpatients with the verified diagnosis of functional constipation (FC) according to Rome criteria IV.

Materials and methods. The study involved 30 outpatients with FC aged 33-59 years (mean age 47.6±5.9 years), with an average disease duration of 14.9±4.8 years, who were treated with the LACTOFOR® complex during 28 days: the first 5 days – 2 sachets per day, followed by 1–2 sachets per day. The treatment effectiveness was assessed by the dynamics of defecation frequency, the feces according the Bristol scale, the assessment of pain syndrome and flatulence on the visual analogue scale, the hydrogen breath test (HBT) with lactulose. Patients' status and quality of life were assessed with the use of specialized patient questionnaires (PAC-SYM – Patient Assessment of Constipation Symptoms and PAC-QoL – Patient Assessment of Quality of Life questionnaire).

Results. The administration of LACTOFOR® complex to patients with FC promoted the increase of bowel movements' frequency (after 28 days of observation, 100% of patients reported daily bowel movement, lack of tension and incomplete emptying) and normalization of stool character, which was confirmed by an increase in stool scores according to the Bristol scale (2.07±0.4 vs 3.42±0.25; $p<0.05$). The effects of LACTOFOR® complex on the reduction of FC symptoms has been established, in particular, a decrease in the intensity and severity of flatulence in 1.9 times ($p<0.01$), as well as painful abdominal syndrome in 2.1 times ($p<0.01$). There was also a clear positive trend in PAC-SYM and quality of life (PAC-QoL) indicators. Reduction of HBT at all intervals of the test confirmed the positive effect of the LACTOFOR® complex on reducing the severity of the bacterial overgrowth syndrome.

Conclusions. The administration of LACTOFOR® complex to patients with FC promoted the increase of bowel movements' frequency, normalization of stool character; it resulted in the reduction of intensity and severity of flatulence, painful abdominal syndrome, as well as improvement of the quality of life.

Key words: functional constipation, LACTOFOR® complex, clinical observation.

INTRODUCTION

Functional gastrointestinal disorders are widespread in the general population. One of the manifestations of these disorders is functional constipation (FC). The overall prevalence is 16% among adults. There is evidence that constipation is more common

in people over 60 years of age - 36% [11]. It is traditionally believed that chronic constipation, in particular functional constipation, does not affect the life expectancy of a human, but significantly impairs its quality compared to patients with diabetes, hypertension and depression [4].

Constipation is considered functional only in the absence of anatomical or physiological cause and is diagnosed according to the Roman Criteria IV (2016) [2, 11]. Particular attention is paid to the following symptoms: bowel movement less than 3 times a week, increased faecal density (type 1–2 according to the Bristol scale), the need for exertion, incomplete stool and/or rectum blockage, the need for palpation. The symptoms are diagnostically significant if they are manifested at least 25% of bowel movements. FC is diagnosed in the presence of any two of the above symptoms, which persist over the last 3 months and a total duration of disorders is more than 6 months [2, 11, 15, 16].

The leading etiological factor of chronic idiopathic constipation is considered to be individual hereditary predisposition. The predominant causes of temporary (situational) FC include changes in living conditions, food and diet, changes in defecation conditions ("tourist constipation"), emotional stress, pregnancy, bed rest, and intake of drugs reducing intestinal motility [11].

FC is a complex problem. There are the dangerous conditions that occur on the background of FC: colitis, rectal and anal fissures, haemorrhoids and varicose vein, chronic intoxication of the body, metabolic disorders, and the formation of solid faecal stones (faeces) with possible damage to the integrity of the bowel. There is a link between FC and poor quality of life. Patients with chronic FC are more likely to suffer from depression and anxiety disorders, and more likely to develop stress-associated diseases [11]. Considering the spread of FC and the complexity of its course, correction of this pathological condition is an urgent task of modern gastroenterology.

According to the Roman Criteria IV, chronic constipation therapy should be comprehensive and begin with lifestyle modification, namely, increasing physical activity and changing the diet (increased dietary fiber content and consuming sufficient fluid) [6, 11]. However, these measures do not always contribute to the normalization of bowel movements in humans. Therefore, more than 85% of patients start to take laxatives on their own, and 66% of them are dissatisfied with the results of self-medication [7].

Drug therapy for chronic constipation (especially functional constipation) is carried out using laxatives, which differ in mechanism of action. Usually osmotic laxatives (lactitol, lactulose, polyethylene glycol) are used, but in case of insufficient efficiency irritant laxatives (senna leaves and fruits, buckthorn fruits, bisacodyl, picosulfate sodium) are used [16]. A significant disadvantage of such group of preparations is the excessive irritating effect on the intestine. Sometimes it causes acute pain, as well as the synthesis and production of inflammatory prostaglandins, which are the main factors

in the inflammatory process. Addiction and dependence may develop due to prolonged use of irritant laxatives [11, 14]. Considering the better tolerability, safety and efficacy, the preference is therefore given to the use of osmotic laxatives, which action is based on the physiological stimulation of the passage of the bowel contents.

One of such laxatives is lactitol (4-o-α-D-galactic-topiranosyl-D-glucitol), a synthetic disaccharide that is not digested by digestive enzymes and reaches the colon when given orally. Lactitol is metabolized by the microflora of the proximal colon with the formation of short-chain fatty acids (oil, acetic, propionic, lactic). Increasing the concentration of these acids contributes to as follows: 1) lower pH in the lumen of the intestine; 2) increase in osmotic pressure, which provides activation of the propulsive peristalsis of the colon; 3) increase in the volume of feces and their dilution due to water retention, which improves their passage through the intestine.

Butyric acid is an energy substrate for enterocytes, which enhances the intestinal smooth muscle contractions [1, 4]. In addition, lactitol stimulates the growth of obligate intestinal microflora, in particular lactobacilli (*Lactobacillus bifidus, L. acidophilus*) and bifidobacteria (*Bifidobacteria spp*.) and inhibits the growth of proteolytic bacteria of *Enterobacteria* and *Enterococci* exhibiting bacterial properties.

A series of randomized clinical trials (RCTs) highlighted in a meta-analysis [13] established high efficacy and good tolerability of lactitol in patients with FC. Its distinctive laxative properties at a daily dose of 20 g or more are proved. According to the trails lactitol is more effective than osmotic laxative –lactulose. In addition, lactitol is statistically significantly superior to lactulose by most characteristics. Lactitol has better organoleptic properties and unlike lactulose it has no side effects (flatulence, intestinal colic, excessive flatulence), which provides higher compliance in patients with functional constipation.

In addition, the prebiotic effect of lactitol is very important in the effective treatment of FC. It has been clinically proven that lactitol has a positive effect on the intestinal microflora in adult patients with FC in history, which was manifested by a statistically significant increase of bifidobacteria count, levels of propionic and butyric acids, as well as a tendency to decrease the number of *Enterobacteria* [10]. Lactitol provides the antagonism of lactobacilli and bifidobacteria with pathogens of *Bacteroides, Clostridium, Salmonella, Staphylococcus and Escherichia coli* species, which is statistically shown by the significant inhibition of the growth of these pathogens [9]. Thus, lactitol is an osmotic laxative with proven clinical efficacy, pronounced prebiotic effect, good tolerability and high adherence to treatment in patients with FC.

In the pharmaceutical market of Ukraine, lactitol is presented as part of the composition of LACTOFOR® (by Ananta Medicare), which is available in the form of oral sachet. In addition to lactitol, the composition of LACTOFOR contains simethicone, *Lactobacillus acidophilus*, folic acid and cyanocobalamin [3]. These ingredients provide a comprehensive approach to solving the problem of FC. The pronounced laxative

effect of lactitol is supplemented by the probiotic effect of *Lactobacillus acidophilus*. A significant decrease in gassing and excessive flatulence in the intestine occurs due to the surfactant properties of simethicone [12]. The inclusion of folic acid and cyanocobalamin in the composition provides a long-lasting positive effect on the bowel's functional state, which is very important in chronic gastrointestinal disorders. Therefore, the clinical interest in the efficacy and safety of the use of LACTOFOR® in patients with FC is relevant.

Objective is to study the efficacy and tolerability of the LACTOFOR® complex (Ananta Medicare) in outpatients with the verified diagnosis of functional constipation (FC) according to Rome criteria IV.

MATERIALS AND METHODS

30 outpatients with FC were involved in an open clinical trial. Criteria for involvement in trial were as follows: availability of verified diagnosis of FC (according to Roman Criteria IV); complaints about FC at the time of involvement in the trial; no contraindications to the use of LACTOFOR®; obligation to follow the treatment and examination protocol; informed consent.

During the study period of 28 days, all patients took LACTOFOR according to the following regime: the first 5 days - 2 sachets a day, then – 1-2 sachets a day.

Performance criteria were assessed by dynamics of the bowel movements' frequency (on 7th, 14th, 21st, 28th day of intake), type of faeces according to the Bristol Stool Chart, pain syndrome and flatulence according to the Visual Analogue Scale (VAS), the result of hydrogen breath test (HBT) with lactulose. Patient status and quality of life were assessed by using specialized questionnaires (PAC-SYM (Patient Assessment of Constipation Symptoms) and PAC-QoL (Patient Assessment of Constipation Quality of Life questionnaire). The tolerability and the presence of adverse reactions were monitored during the observation period (according to the individual survey and the patient's diary).

Statistical processing of the results was performed by using GraphPad Prism version 5.00 (GraphPad Software, Inc). In case of normal distribution of the data, the results were available as arithmetic mean (M) and its error (m), and 95% confidence interval (CI). Intergroup differences were assessed by using a paired Student's t-test.

RESULTS AND DISCUSSION

Among the surveyed patients, 26 (86.7%) women prevailed. Patients age was 33-59 years (mean (47.6 ± 5.9) years). The average duration of the disease is (14.9 ± 4.8) years. Due to the development of FC 22 (73.3%) patients reported irregular nutrition,

12 (40%) - poor diet with low dietary fiber content, consumption of a small amount of fluid per day, 24 (80%) - inactive lifestyle, 27 (90 %) - psycho-emotional stress, 3 (10%) - medications intake(antibiotics). 5 (16.6%) patients were overweight. Mean indexes of body mass index and waist circumference were (26.1 ± 5.3) kg/m^2 and (79.6 ± 14.2) cm, respectively.

On initial examination, the overall condition of the patients was assessed as satisfactory. 28 (93.3%) patients complained of the presence of defecation frequency less than 3 times a week, 22 (73.3%) patients – feelings of exertion and incomplete stool, 24 (80%) patients – flatulence, 23 (76.7%) patients – pain, 13 (43,3%) patients – irritability. The type of feces on the Bristol scale averaged the 2nd type (2.07 ± 0.40). The need for specific manipulations to facilitate the act of defecation (finger evacuation, pelvic floor support) was reported by 12 (40%) patients, of which 8 (26.6%) used enemas more than once a week.

During the initial examination of patients with FC, the assessment of flatulence according to VAS averaged (5.14 ± 0.59) points (95% CI 3.92-6.36 points), and abdominal spastic and bursting pains, which disappeared after defecation – (2.85 ± 0.41) points (95% CI 2.0-3.71). The total number of symptoms according to PAC-SYM questionnaire was (22.61 ± 1.28) points (95% CI 19.96-25.25), and was accompanied by a decrease in the quality of life of the patients evaluated by the PAC-QoL questionnaire and made (57 , 86 ± 3.17) points (95% CI 61.33-64.38). In 21 (70%) patients, the parameters of HBT were increased by 60-120 min. This proved the increase in the amount and level of metabolic activity of anaerobic bacteria against the background of impaired intestinal microflora.

Thus, the results of the analysis of demographic and anamnestic parameters of the participants have revealed that the severity of clinical manifestations of FC was dependent on the psycho-emotional state, regimen and quality of nutrition, which directly affects the quality of life of patients and requires the development of effective measures that would facilitate the condition of patients.

After 28 days of the study, all patients reported an increase in frequency and the presence of daily bowel movements (7.84 ± 1.27 vs. 1.8 ± 0.51; $p < 0.001$), no exertion feelings, no feelings of incomplete stool and reduction of irritability (Fig. 1).

The use of LACTOFOR contributed to the normalization of the defecation, proved by the appropriate increased score in the Bristol scale (see Fig. 1). On the 4-6th day a tendency for positive changes in the nature of the feces was observed (increased frequency from 2.07 ± 0.4 to 3.07 ± 0.33; $p = 0.38$); on the 28th day the parameter was significantly improved to 3.42 ± 0.25 (95% CI 2.9-3.95; $p < 0.05$). According to patients' report there was no need for specific manipulation to facilitate the act of defecation.

During the first 4-5 days there was a tendency to decrease pain according to VAS (Fig. 2): 2.85 ± 0.41 and 2.46 ± 0.3 ($p = 0.08$), respectively. Starting from the 6-8th day of

using LACTOFOR, a statistically significant decrease in the intensity of pain of the abdominal syndrome was 2.1 times ($p < 0.01$) – 1.35 ± 0.3 (95% CI 0.73-1.98) ; $p < 0.05$) on day 28.

Similar dynamics was established for the intensity of flatulence (see Fig. 2), which on the 5-6th day was not significantly different from the original data ((5.14 ± 0.59) and (4.57 ± 0.46) points; $p > 0.05$). At the beginning of intake (1st to 3rd day), 12 (40%) patients reported a mild increase in flatulence, which can be explained by the effect of the first passage of lactitol in an environment of excess bacterial growth.

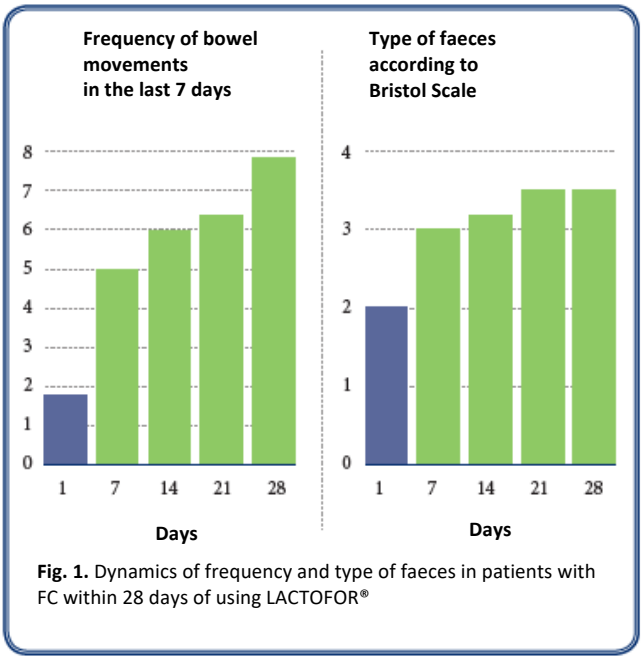

Fig. 1. Dynamics of frequency and type of faeces in patients with FC within 28 days of using LACTOFOR®

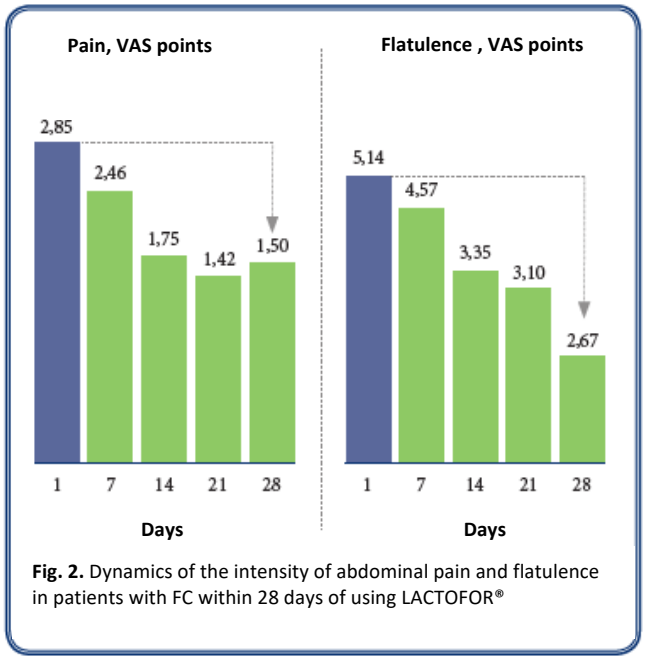

Fig. 2. Dynamics of the intensity of abdominal pain and flatulence in patients with FC within 28 days of using LACTOFOR®

Starting from the 4th day, flatulence has decreased significantly. After 28 days of administration of LACTOFOR, this parameter significantly decreased by 1.9 times ($p < 0.05$) that corresponds to the physiological norm. Within 28 days, the positive dynamics of PAC-SYM symptom score were observed (22.6 and 8.9 points at the 1st and 2nd visits, respectively). The number of symptoms of FC decreased by 2.5 times ($p < 0.001$) compared with the corresponding parameters at the 1st visit. This proves the complexity of the action due to the multicomponent composition (Fig. 3).

Thus, the administration of LACTOFOR within 28 days to patients with FC contributed to a complete and statistically significant reduction in clinical manifestations of FC, in particular the normalization of the frequency and quality of bowel movements, the elimination of the main symptoms of functional constipation – abdominal pain, flatulence and associated discomfort, as well as improved feelings of a patient.

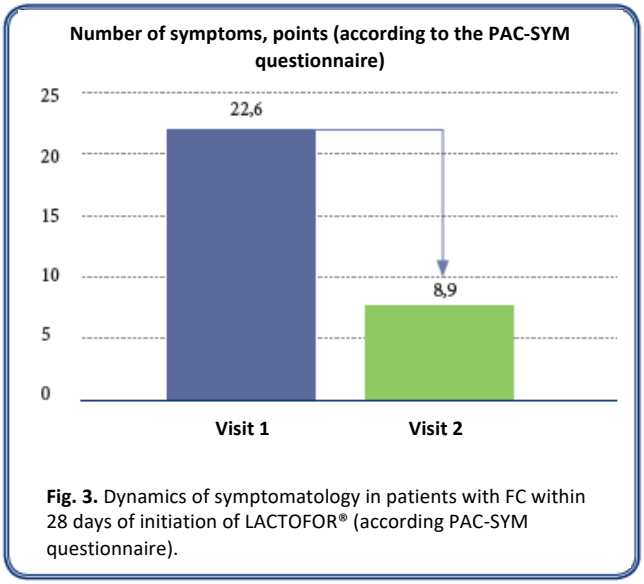

Fig. 3. Dynamics of symptomatology in patients with FC within 28 days of initiation of LACTOFOR® (according PAC-SYM questionnaire).

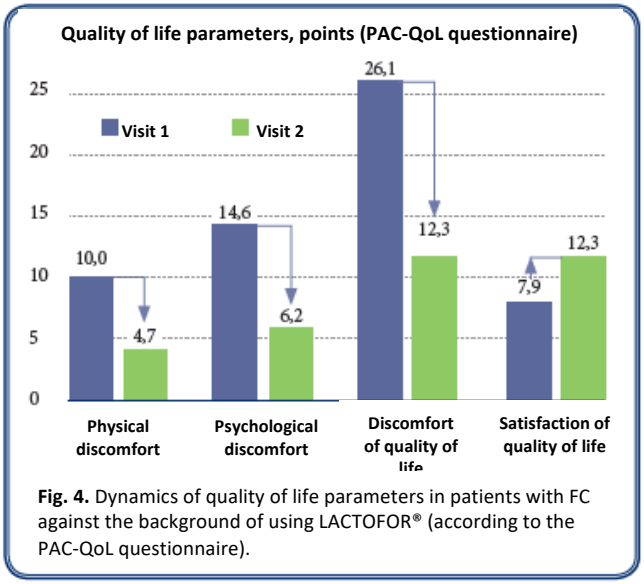

Fig. 4. Dynamics of quality of life parameters in patients with FC against the background of using LACTOFOR® (according to the PAC-QoL questionnaire).

Equally important is the fact that the complex laxative effect shows the direct positive effect on the quality of life in patients with FC. This is established by the results of the participants' survey using a standardized PAC-QoL questionnaire. The use of LACTOFOR at the beginning and after 28 days made it possible to accurately assess the level of physical, psychological discomfort, anxiety and satisfaction levels in the patients (table).

According to the results of the study, the total PAC-QoL score was significantly ($p < 0.001$) 1.7 times lower than at the first visit. It is proved by a statistically significant improvement in overall quality of life and its individual components (see table). After 28 days of intake, a decrease in physical discomfort was 2.1 times ($p < 0.01$), psychological discomfort – 2.3 times ($p < 0.001$), discomfort of quality of life– 2.1 times ($p < 0, 01$), and the satisfaction of quality of life was increased by 1.5 times ($p < 0.01$) (Fig. 4).

Thus, the complexity of the positive effect of LACTOFOR® in patients with FC is manifested both at the level of individual symptoms and at the level of subjective feelings of well-being and satisfaction with the quality of life. The results obtained with regard to the positive effect of LACTOPHOR® on the quality of life of patients with FC indicate that its use can prevent the development of psychological disorders associated with chronic constipation (prolonged stress, emotional lability, anxiety, depression, etc.).

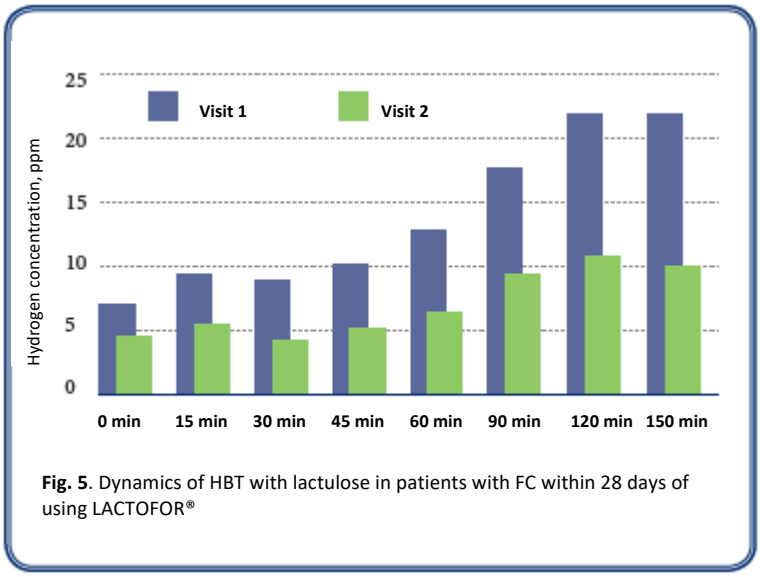

Fig. 5. Dynamics of HBT with lactulose in patients with FC within 28 days of using LACTOFOR®

Instrumental methods confirmed the positive effect of LACTOFOR® on the symptomatology of functional constipation, namely the decreased concentration of hydrogen in the air exhaled by patients (Fig. 5). HBT scores were declined at all test intervals, indicating the positive effect of LACTOFOR® on reducing the growth rate of conditionally pathogenic microflora associated with impaired intestine microbiocenosis. This was confirmed by a statistically significant increase in the total number of *Escherichia coli* by 1.25 times ((4.33 ± 0.39) × 107 CFU/g (95% CI 3.5-5.15) and (5.42 ± 0.20) × 107 CFU/g (95% CI 4.99-5.85; p <0.01), respectively. A pronounced positive effect on the intestinal microbiota can be caused by the synbiotic action of the active components of LACTOFOR®: lactitol prebiotic and Lactobacillus acidophilus probiotic. Its clinical use in patients with FC associated with intestinal dysbiosis is promising. Considering that intestinal microflora disorders are associated with functional constipation in most patients, the use of LACTOFOR in the treatment regime is the optimal option of therapy, which solves the problem comprehensively.

Table. Quality of life parameters according to PAC-QoL questionnaire (M ± m)

Parameters, points	**Visit 1**	**Visit 2**
Overall quality of life	57,86±3,17	33,61±1,91**
Physical discomfort	10,0±1,9	4,7±1,7*
Psychological discomfort	14,6±3,7	6,2±1,5*
Discomfort of quality of life	26,1±3,5	12,3±2,6*
Satisfaction of quality of life	7,9±1,6	12,3±3,1*

*Note. The difference between the parameters for the 1st visit is statistically significant: * $p \leq 0.01$; ** $p \leq 0.001$.*

Considering the mild, physiological, laxative effect, the ability to almost completely eliminate the symptoms of FC and the complex pre- and probiotic action, the use of LACTOFOR® in patients with gastrointestinal disorders with symptoms of constipation may prevent the development of constipation under such conditions.

The tolerance monitoring of LACTOFOR® in patients with FC during the entire observation period has proved the absence of adverse reactions, individual intolerance, the development of severe and unexpected side effects, worsening of the general condition, failure to follow the regimen and rejection of patients to participate the study. Thus, the use of LACTOFOR® in patients with FC may be considered as safe and well tolerated.

CONCLUSIONS

The appointment of LACTOFOR® for patients with functional constipation contributes to increased frequency of bowel movements (after 28 days of observation, all patients reported daily bowel movements, the absence of discomfort feelings and incomplete defecation feeling) and normalization of the bowel movements, which is confirmed by a statistically significant increased defecation according to the Bristol scale (2.07 ± 0.4 and 3.42 ± 0.25; $p < 0.05$).

The positive effect of LACTOFOR® on reduction of FC symptoms was established, in particular decrease of intensity and expressiveness of flatulence by 1.9 times ($p < 0.01$) and abdominal pain syndrome by 2.1 times as well ($p < 0.01$).

Within the 28 days of using LACTOFOR®, the positive dynamics was observed by using PACSYM and Quality of Life Questionnaire (PAC-QoL), confirming the complex effect both at the level of individual symptoms and at the level of subjective sense of well-being and satisfaction with quality of life.

Reduction of hydrogen respiratory test at all test intervals has confirmed the positive effect of LACTOFOR® on reducing the severity of the bacterial overgrowth syndrome.

During the observation, good tolerability of LACTOFOR® was noted by patients with FC. There were no side effects. LACTOFOR is safe for the patient.

The obtained results prove the expediency of use of LACTOFOR® in the treatment regime of patients with functional gastrointestinal disorders accompanied with the symptoms of constipation.