УДК 616.34-002-082
https://doi.org/10.20538/1682-0363-2021-3-120-128

Adherence to treatment in patients with inflammatory bowel disease

Andreev K.A., Gorbenko A.V., Skirdenko Yu.P., Nikolaev N.A., Livzan M.A., Bikbavova G.R., Fedorin M.M.

Omsk State Medical University
12, Lenina Str., Omsk, 644099, Russian Federation

ABSTRACT

Inflammatory bowel disease (IBD) is a common pathology that reduces the quality and duration of a patient's life. The cornerstone of treatment of IBD patients is polypharmacotherapy based on the use of salicylates, antibiotics, immunomodulatory and biological drugs, and topical dosage forms. Multicomponent treatment has shown to reduce the quality of life and negatively affect adherence to drug therapy in IBD patients.

One of the leading causes of treatment failure is low treatment adherence, which leads to disease progression, disability, and increased financial costs. Currently, there are many factors that affect adherence to therapy, some of them are modifiable, which creates opportunities to improve the effectiveness of existing medical interventions. However, the available data on the level of adherence in IBD patients are not numerous and homogeneous, so a low level of adherence to drug therapy in IBD patients is registered in 7–72% of cases.

An important issue in understanding adherence in IBD patients is a lack of research on the level of adherence to counselling and lifestyle modification. However, the course of IBD, treatment features related to the duration of therapy and necessary lifestyle modifications (nutrition), as well as regular monitoring of laboratory and instrumental parameters determine the need to assess adherence to lifestyle modification and counselling along with adherence to drug therapy.

Key words: inflammatory bowel disease, ulcerative colitis, Crohn's disease, treatment adherence, quality of life.

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

Source of financing. The research was carried out with the state support for the leading scientific schools of the Russian Federation (Grant No. SS-2558.2020.7, Agreement No. 075-15-2020- 036 of 17.03.2020 "Development of Health-Preserving Technology for a Comorbid Gastroenterological Patient Based on Adherence Control").

For citation: Andreev K.A., Gorbenko A.V., Skirdenko Yu.P., Nikolaev N.A., Livzan M.A., Bikbavova G.R., Fedorin M.M. Adherence to treatment in patients with inflammatory bowel disease. *Bulletin of Siberian Medicine.* 2021; 20 (3): 120–128. https://doi.org/10.20538/1682-0363-2021-3-120-128.

Приверженность лечению больных воспалительными заболеваниями кишечника

Андреев К.А., Горбенко А.В., Скирденко Ю.П., Николаев Н.А., Ливзан М.А., Бикбавова Г.Р., Федорин М.М.

Омский государственный медицинский университет (ОмГМУ)
Россия, 644099, г. Омск, ул. Ленина, 12

✉ *Gorbenko Aleksander V.,* e-mail: prime.dr.alex@gmail.com

РЕЗЮМЕ

Воспалительные заболевания кишечника (ВЗК) – это распространенная патология, снижающая качество и продолжительность жизни пациента. Краеугольным камнем лечения больных ВЗК является полифармакотерапия, основанная на применении салицилатов, антибиотиков, иммуномодулирующих и биологических препаратов, использовании местных лекарственных форм. Показано, что сложные схемы лечения снижают качество жизни и отрицательно сказываются на приверженности лекарственной терапии больных ВЗК.

Одной из ведущих причин неэффективности лечения является низкий уровень приверженности, что приводит к прогрессированию заболевания, инвалидизации и увеличению финансовых затрат. В настоящий момент известно много факторов, влияющих на приверженность терапии, часть из них модифицируема, что создает возможности для повышения эффективности существующих медицинских вмешательств. Однако имеющиеся данные об уровне приверженности больных ВЗК не отличаются многочисленностью и однородностью. Так, низкий уровень приверженности лекарственной терапии больных ВЗК регистрируется в 7–72% случаев.

Важной проблемой понимания приверженности больных ВЗК является отсутствие исследований об уровне приверженности медицинскому сопровождению и модификации образа жизни. Тогда как течение ВЗК и особенности лечения, связанные с длительностью терапии, необходимой модификацией образа жизни (питания), а также регулярный контроль лабораторных и инструментальных параметров диктуют необходимость оценки приверженности модификации образа жизни и медицинскому сопровождению наряду с приверженностью лекарственной терапии.

Ключевые слова: воспалительные заболевания кишечника, язвенный колит, болезнь Крона, приверженность, качество жизни.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Публикация подготовлена при государственной поддержке ведущих научных школ Российской Федерации (грант НШ-2558.2020.7, соглашение № 075-15-2020-036 от 17.03.2020 «Разработка технологии здоровьесбережения коморбидного больного гастроэнтерологического профиля на основе контроля приверженности»).

Для цитирования: Андреев К.А., Горбенко А.В., Скирденко Ю.П., Николаев Н.А., Ливзан М.А., Бикбавова Г.Р., Федорин М.М. Приверженность лечению больных воспалительными заболеваниями кишечника. *Бюллетень сибирской медицины.* 2021; 20 (3): 120–128. https://doi.org/10.20538/1682-0363-2021-3-120-128.

RATIONALE

The evolution of mankind has long gone beyond biology. Socialization, urbanization, and technological progress have brought benefits and made life comfortable. The development of science and technology has made it possible to improve methods of diagnosis, treatment, and disease prevention. However, incidence of diseases in general is not reducing, but their spectrum is changing. Thus, in developed countries, lifestyle-associated diseases are increasingly common [1]. Inflammatory bowel disease (IBD) is a striking consequence of modern lifestyle.

To date, evidence of the influence of environmental factors on the state of the intestinal mucosa, microbiota composition and its interaction with the intestinal wall has been accumulated, which triggers a progressive immune response in genetically predisposed individuals [2]. The pathogenesis of inflammatory bowel diseases is not fully understood. It is known that in IBD under the influence of a complex of factors (genetic, microbial, dietary, and psychological), dysfunction of the intestinal barrier develops, which contributes to translocation of microorganisms and products of microbial origin and leads to activation of the immune response. The immune-mediated reaction to the intestinal microflora is considered the basis of pathogenesis [3].

According to some data, improvement of sanitary and hygienic living conditions in childhood leads to a decrease in the antigenic effect on the body, which can cause the development of hyperreactivity upon contact with microorganisms later in adulthood [4]. Diet was shown to be an important environmental factor in the course of IBD [2]. Lack of time, stress, and hypodynamia have significantly changed our diet over the past 30 years [5], with more ready-to-

eat foods, flavor enhancers, sugar and sugar substitutes, high-calorie foods, animal proteins, and less dietary fiber [6].

Few diseases affect human life as dramatically as IBD [7]. The debut of the disease occurs at a young age (20–30 years), when a person lives an active social life [3]. The disease proceeds for a long period of time and causes severe pain, with constantly alternating periods of remission and relapse [8]. The main complaint of patients is chronic diarrhea, with stool frequency up to 20 times a day during day and night [3]. Ulcerative colitis (UC) and Crohn's disease (CD) adversely impact a patient's quality of life, increase the risk of colorectal cancer, the incidence of which is 15% after 30 years of the disease, and often lead to disability [9].

MAIN PART

Multicomponent pharmacological therapy, based on the long-term use of salicylates, antibiotics, and immunomodulatory and biological agents, is pivotal in treatment of IBD [10]. However, these groups of drugs are characterized by a number of side effects, such as nausea, vomiting, fever, aggravation of diarrhea, elevated blood pressure, seizures, joint and muscle pain, disruption of growth processes in children, and development of infectious complications [11]. In addition, researchers from Italy found that the use of topical drugs in the form of suppositories and rectal foams is associated with low adherence compared with oral forms, with 68% and 40% of non-compliant patients in the respective groups [12]. Multifaceted clinical presentation, complex treatment regimen, and its undesirable effects pose difficulties for an active social life of the patient [3].

All of these factors significantly reduce the quality of life and negatively affect adherence to drug therapy [7]. Patients' adherence to treatment in all chronic diseases decreases over time, which is also caused by a need for chronic drug administration [13]. In the outpatient setting, non-compliance in patients with chronic diseases is 30–60% [14]. Low adherence to treatment is one of the main reasons for low efficiency of chronic disease therapy and has a number of negative economic consequences for both the patient and the healthcare system [15].

Therefore, public healthcare systems spend vast financial resources on treating patients with IBD. For example, six-month treatment of one IBD patient costs € 2,500 in Belgium, while the cost of a year-long treatment of one IBD patient exceeds £ 2,000 in the United Kingdom [16]. In the United States, treatment of one IBD patient costs about $35,000, which totals about $2 billion for all the patients in the country [17]. In Russia, there is no official information on the estimated cost of treatment for patients with IBD [18]. However, in 2019, researchers from Tatarstan calculated that treatment of one IBD patient cost from 50,000 to 200,000 rubles per year, depending on the severity of the disease, type of care, and disease duration, with calculations carried out on the basis of tariff agreements with the compulsory medical insurance fund [19].

A survey of 100 patients with IBD, carried out by M.F. Vladimirsky Moscow Regional Clinical Research Institute, revealed that 40% of the respondents violated the prescribed treatment regimen, and the patients mentioned high treatment costs as one of the main reasons [20]. The patient takes up a considerable part of the treatment cost, which, given difficulties associated with the inability to work full-time, results in a significant financial loss and affects the patient's willingness to undergo treatment [1]. Patients with IBD have to receive life-long pharmacotherapy, which is the cornerstone of therapy [21, 22].

Currently, data on therapy adherence in patients with gastrointestinal pathology remain scarce and heterogeneous. Researchers from London analyzed 17 studies involving 4,322 patients with IBD; lack of adherence to treatment was detected in 7–72% of cases [23]. Treatment of IBD patients includes not only the use of medications, but also dieting, which over time reduces the patients' adherence to therapy in general [24]. At the same time, very few studies have investigated adherence to a new lifestyle (in case of IBD, adherence to a diet).

Adherence is pivotal in treatment of patients with IBD. In a study of a cohort of 99 UC patients who had been in remission for more than six months and were receiving mesalazine maintenance therapy, researchers from the University of Michigan and the University of Chicago concluded that non-compliant patients had a five times higher risk of relapse [25]. Later, researchers from Louisiana conducted a large retrospective study involving 13,062 patients with UC over a 10-year period. It revealed that patients with low adherence had a 60% higher risk of relapse [26]. Researchers from Salford Royal Hospital carried out a similar retrospective study, but

in one group of patients, they periodically changed the form of mesalazine administration. As a result, it was found that the risk of relapse was 3.5 times higher in this group of patients [27].

In addition to a significant impact on therapy effectiveness and reduction of the risk of complications and disability, high adherence to treatment considerably impacts the costs [28]. For example, regular use of salicylates in patients with IBD reduces hospitalization costs by 62%, with a decrease in outpatient care by 13%, in emergency care by 45%, and in total costs of the healthcare system for treating adherent patients by 50% [14]. Thus, increasing patient adherence to treatment is important, according to some data, it is even more important than improving specific treatment methods [24].

In a study conducted in Chelyabinsk, based on the results of a survey of 133 patients with IBD, 58.4% of the respondents were found to have a low level of adherence. We used our own questionnaire to assess the level of adherence. The questionnaire included questions about the reasons for non-compliance with doctor's recommendations. The following social and economic reasons were identified: insufficient financial resources (31.5%), irregular supply of subsidized drugs (26%), and lack of drugs in the pharmacy (14.6%).

As for reasons related to the patient, 49.7% of the respondents mentioned lack of awareness about their disease, 42.2% of the individuals did not believe in the treatment success, 24.5% of the patients expressed fear of "getting addicted" to medications, 12.6% of the patients had doubts about the necessity of therapy, and only 13% of the respondents mentioned forgetfulness. Poor drug tolerance, allergic reactions, and development of adverse effects were noted by 3.8%, 2.7%, and 6.3% of the respondents, respectively [29]. Analyzing the reasons for low adherence, it should be noted that most of them are related to the financial, logistical, and informational aspects of the issue, i.e. they can be changed.

The adherence of UC patients is affected by many aspects, including intensity and duration of the disease, treatment cost, adverse events of therapy, individual psychosocial characteristics, and the level of patient-doctor cooperation [30]. Low adherence to treatment can be particularly noted in patients in remission, due to the absence of symptoms. A large number of pills and complicated treatment regimens are believed to be among the main factors determining low adherence [31]. This is confirmed by the results of a survey conducted among 1,595 patients with IBD in the United States. Thus, 65% (944) of the respondents showed low adherence, while the reported causes included inconvenience of taking medications frequently during the day and the use of rectal forms [32].

At Ryzhikh National Medical Research Center of Coloproctology, a study was conducted with 380 patients with active UC. It revealed that 79.1% of the patients who took a daily dose of mesalazine once a day and 75.7% of the patients who took a daily dose of mesalazine three times a day went into clinical remission. On this basis, researchers recommended to give preference to a single daily dose of oral mesalazine, as this has a positive effect on the adherence level and will ultimately increase the effectiveness of the entire treatment [33].

In terms of the impact on adherence, the total number of medications taken per day is also important. Patients taking four or more medications every day have a higher rate of poor adherence than those taking fewer medications per day (60% and 40%, respectively) [34]. Currently, this becomes particularly relevant given the prevalence of comorbidity among patients.

Scholars from the Research Institute of Physiology and Fundamental Medicine found that there are manifestations of nonalcoholic fatty liver disease in half of IBD patients. Abdominal obesity, metabolic syndrome, age over 40 years, and arterial hypertension were the main factors associated with the presence of nonalcoholic steatohepatitis in IBD patients. CD with comorbid nonalcoholic steatohepatitis was characterized by a need for a higher dose of azathioprine [35]. Assessment of the comorbid background in patients with IBD is a serious task in the joint work of a doctor and a patient, when selecting an individualized treatment regimen.

According to C. Selinger et al., in Australia, non-compliance with maintenance therapy was detected in 30% of IBD patients. At the same time, among patients receiving biological therapy, low adherence was detected only in 5.3% of cases [36]. Researchers from the University Hospital of Nancy Brabois conducted a systematic review to analyze the level of adherence to therapy with tumor necrosis factor inhibitors (anti-TNF). According to 13 studies involving 93,998 patients with IBD, the overall adherence was 82.6% [37].

Therefore, the use of biological therapy in treatment of inflammatory bowel diseases can be considered as a factor associated with high adherence to treatment. The revealed fact needs to be studied more thoroughly. A lack of adherence to anti-TNF therapy leads to subsequent immunogenicity and a lack of a response to the ongoing biological therapy [14].

The study of socio-psychological factors as modifiers of adherence levels showed that among non-compliant patients, there are considerably more employed people (85.9%, $p < 0.05$) at the age of 40–49 years (25.6%, $p < 0.05$), with completed secondary education (56.4%, $p < 0.05$), with an identified non-constructive model of child – parent relationships (85.9%, $p < 0.05$), and in an unfavorable, conflict family environment (18.2%, $p < 0.05$) [38]. Previously, researchers in Italy found that insufficient adherence was significantly more common in the group of patients under 40 years (43% as opposed to 34%). Disease duration of less than 5 years was also characterized by lower adherence (24% as opposed to 15%). It should be noted that with these two factors combined the non-compliance level reached 75% [39]. As for gender differences, there is no single opinion. In some studies, male gender was found to be a predictor of low adherence, while other studies revealed female gender to be the one, and some studies found no significant differences between men and women at all [34, 40, 41].

Anxiety disorders in gastroenterological patients undergoing treatment for a long time reduce adherence to therapy. Changing the patient's mental status and a proactive attitude of the attending doctor were found to have a positive effect on the patient's compliance [42]. Complete understanding of the disease and clear statement of therapy goals and objectives have a positive effect on the patient's readiness for counselling and lifestyle modifications, ultimately increasing the level of adherence to treatment [43].

Researchers at Cincinnati Children's Hospital Medical Center examined the quality of life and adherence in 36 adult patients with IBD. As a result, a correlation was found between insufficient adherence to azathioprine and a poor quality of life [44]. In addition, a research team from Hungary carried out a study involving 592 patients with IBD and did not reveal a relationship between the level of adherence and the quality of life, but found a higher incidence of disability in low adherence [45]. Australian researchers found that low adherence to drug therapy is one of the most significant risk factors for disability in patients with IBD ($p < 0.0001$) [46].

In issues of adherence to treatment, a well-established partnership between a patient and a doctor and their effective communication are often crucial in determining the level of adherence to therapy [12]. The doctor – patient interaction has an enormous impact on the efficacy of therapy and reduces the treatment cost. It was found that failure to schedule a follow-up visit by the attending doctor is accompanied by greater development of depression in patients, reduces the level of trust in the physician, and worsens adherence, eventually leading to refusal from the recommended treatment [47, 48].

The Selecting Therapeutic Targets in Inflammatory Bowel Disease committee (STRIDE) identified achievement of a high quality of life as the main goal of treating IBD patients. A decisive approach to achieving remission and tertiary prevention of IBD patients is the treat-to-target concept (T2T), based on patient's subjective needs [49]. Individual therapy regimens are designed, taking into account the extent of the lesion, the severity of the disease, tolerability of pharmacotherapy, lifestyle, and diet therapy. Patients with IBD are required to control semiotics, and doctor's work is focused on biochemical, morphological, and endoscopic criteria of disease intensity [50].

There are two groups of methods for assessing adherence. Direct assessment methods include blood biochemistry for detecting the content of drugs and their metabolites. Indirect methods include pill counts, prescription dispensing logs and patient medication logs, questionnaires, and the use of electronic devices. All methods are far from perfect, but adherence questionnaires are most commonly used. The use of customized questionnaires to assess adherence makes it difficult to assess the results and makes it almost impossible to compare them with others.

Uniform questionnaires facilitate analysis and comparison of obtained data. The first scale used in patients with IBD was the modified Morisky – Green – Levine Medication Adherence Scale [51]. However, it shows only the level of adherence to drug therapy, without considering other components of compliance, such as adherence to counselling and lifestyle modifications, the assessment of which is critical for understanding adherence to IBD therapy

[52]. The Quantitative Assessment of Treatment Adherence Questionnaire (QAT-25) recommended by the Russian Scientific Medical Society of Therapists allows for quantitative (i.e., as a percentage) calculation of adherence to drug therapy, lifestyle modification, and counselling separately and has high rates of specificity (78%), sensitivity (94%), and reliability (94%), according to an independent assessment [52].

Currently, there are no generally accepted methods to increase the level of adherence. Methodological systems for teaching patients, digital reminders for taking medications, and the most effective logistics of drug supply for the convenience of patients are actively used abroad [53, 54]. Australian researchers found that an individual consultation of non-adherent IBD patients with a clinical pharmacologist regarding drug therapy increased their adherence to the level of the initially adherent group and had maintained for at least 15 months [55].

According to a meta-analysis conducted by scientists from North Carolina, regarding reminder systems (text and voice reminders on the phone, pill boxes, etc.), a significant increase in adherence was observed compared with controls, regardless of the reminder method used [56]. In Russia, the most widespread method of influencing adherence has been "Health-Promoting Schools", including patients with IBD [53]. However, there are no data showing long-lasting results in IBD patients.

CONCLUSION

The literature review revealed that high adherence to treatment in IBD patients increases therapy effectiveness, reduces the risk of relapses and complications, and significantly affects financial savings for both public healthcare systems and patients. According to the combined research results, adherence to drug therapy in IBD patients is low, whereas adherence to lifestyle modification and counselling in patients with IBD has not been studied at all. The importance of studying adherence to lifestyle modification in patients with IBD is determined by a great contribution of diet therapy, but patients' readiness for it is currently unknown.

The study of adherence to counselling will make it possible to understand readiness for regular visits to the doctor and control of clinical, laboratory, and instrumental criteria of the disease course. The overwhelming majority of the revealed reasons for low adherence are potentially modifiable. Possibilities of modifying adherence in IBD patients, both in short and long term, require further study to develop effective algorithms to increase it.

An important factor associated with high adherence is joint work of the doctor and the patient during selection of an individual treatment regimen based on personal needs of the IBD patient and assessment of the comorbid background in order to improve the patient's quality of life. A comprehensive approach to the study of adherence to treatment in IBD patients will help to unify methods for assessing and analyzing the level of compliance and design methods to impact it.

REFERENCES

1. Knyazev V.O., Shkurko V.T., Fadeeva A.N., Bakulin G.I., Bordin S.D. Epidemiology of chronic inflammatory bowel disease. Yesterday, today, tomorrow. *Experimental and Clinical Gastroenterology.* 2017; 139 (3): 4–12 (in Russ.).
2. Cuiv P.O., Begun J., Keely S. Towards an integrated understanding of the therapeutic utility of exclusive enteral nutrition in the treatment of Crohn's disease. *Food Funct.* 2016; 7 (4): 1741–1751. DOI: 10.1039/C5FO01196E.
3. Ivashkin V.T., Shelygin Yu.A., Belousova E.A., Abdulganieva D.I., Alekseeva O.A., Achkasov S.I., Valuiskikh E.Yu., Vardanyan A.V., Veselov A.V., Veselov V.V., Golovenko O.V., Gubonina I.V., Zhigalova T.N., Kashnikov V.N., Knyazev O.V., Makarchuk P.A., Moskalev A .I. Project: Clinical guidelines for the diagnostics and treatment of ulcerative colitis. *Koloproktologia.* 2019; 18 (4): 7–36 (in Russ.). DOI: 10.33878/2073-7556-2019-18-4-7-36.
4. Fiocchi C. Etiopathogenesis of inflammatory bowel diseases. *Koloproktologia.* 2015; 51 (1): 5–20 (in Russ.).
5. Livzan M.A., Nikolaev N.A., Skirdenko Yu.P., Fedorin M.M., Gorbenko A.V., Andreev K.A., Andreeva E.K., Ivanov A.I., Ivakhnenko A.T. Nutritional behavior in the student environment. *Kremlin Medicine Journal.* 2019; 2: 13–16 (in Russ.). DOI: 10.26269/tvs8-by34.
6. Bikbavova G.R., Livzan M.A., Sovalkin V.I., Turchaninov D.V., Lopatina O.E., Tretyakova T.V., Akhramovich A.P., Gordienko T.S. Modern lifestyle and its impact on the ulcerative colitis incidence. *The Russian Archives of Internal Medicine.* 2019; 9 (3): 188–193 (in Russ.). DOI: 10.20514/2226-6704-2019-9-3-188-193.
7. Paulino S., Dias J. The role of nutritional approach in the management of Crohn's disease. *Pediatrics. Suppl.* 2018; 10–16 (in Russ.). DOI: 10.26442/2413-8460_2018.2.10-16.
8. Sovalkin V.I., Akhmedov V.A., Bikbavova G.R., Emelyanova Yu.A. Modern views on prevalence, risk factors, and causes of ulcerative colitis. *Experimental and Clinical Gastroenterology.* 2017; 10 (146): 110–115 (in Russ.).

9. Guseinova Z.K., Taizhanova D.Zh., Tauesheva Z.B., Mandybaeva M.K., Holoshenko A.O. Prevalence and screening diagnosis of colorectal cancer. *Medical sciences.* 2015; 3 (2): 190–197 (in Russ.).
10. Rubin D.T., Ananthakrishnan A.N., Siegel C.A., Sauer B.G., Long M.D. ACG Clinical guideline: ulcerative colitis in adults. *Am. J. Gastroenterol.* 2019; 114 (3): 384–413. DOI: 10.14309/AJG.0000000000000152.
11. Ahmed I., Roy B., Khan S., Septer S., Umar S. Microbiome, metabolome and inflammatory bowel disease. *Microorganisms.* 2016; 4 (2): 20. DOI: 10.3390/microorganisms4020020.
12. D'Incà R., Bertomoro P., Mazzocco K., Vettorato MG., Rumiati R., Sturniolo GC. Risk factors for non-adherence to medication in inflammatory bowel disease patients. *Aliment. Pharmacol. Ther.* 2008; 27 (2): 166–172. DOI: 10.1111/j.1365-2036.2007.03555.x.
13. Nalyotov S.V., Alesinsky M.M., Nalyotova E.N. Compliance of hypertensive patients in the blockade Donbass. Solving the problem in collaboration of a doctor and a pharmacist. 2017: 55 (in Russ.).
14. Kane S., Shaya F. Medication non-adherence is associated with increased medical health care costs. *Dig. Dis. Sci.* 2008; 53 (4): 1020–1024. DOI: 10.1007/s10620-007-9968-0.
15. Mikirtichan G.L., Kaurova T.V., Ochkur O.K. Compliance as a medico-social and ethical problem in pediatrics. *Current Pediatrics.* 2012; 11 (6): 5–10 (in Russ.). DOI: 10.15690/vsp.v11i6.485.
16. Muller-Lissner S.A., Bollani S., Brummer R.J. et al. Epidemiological aspects of irritable bowel syndrome in Europe and North America. *Digestion*. 2001; 64 (3): 200–204. DOI: 10.1159/000048862.
17. Ward F.M., Bodger K., Laly M.G., Heatley R.V. Clinical economic review: medical management of inflammatory bowel disease. *Pharmacol. Ther.* 1999; 13 (1): 15–25. DOI: 10.1046/j.1365-2036.1999.00437.x.
18. Koposova K.A., Khlynova O.V. Project routing patients with inflammatory bowel disease in the Perm region. *Kazan Medical Journal*. 2016; 2: 32–35 (in Russ.).
19. Bezdezhnykh T.P., Fedyaev D.V., Khachatryan G.R., Arutyunov G.G., Gerasimova K.V. Economic consequences of healthcare optimization for IBD patients in the Republic of Tatarstan. *Modern pharmacoeconomics and pharmacoepidemiology*. 2019; 12 (1): 14–26 (in Russ.). DOI: 10.17749/2070-4909.2019.12.1.14-26.
20. Buzunova Yu.M., Belousova E.A. Adherence to the treatment of patients with inflammatory bowel disease. *Gastroenterologiia Sankt-Peterburga*. 2015; 1–2: M5–M5b (in Russ.).
21. Kuvshinova N.Yu. The problem of compliance therapy in different fields of medicine. *Izvestia of Samara Scientific Center of the Russian Academy of Sciences.* 2015; 17 (5–3): 1014–1020. 22 (in Russ.).
22. Parfenov A.I., Kagramanova A.V., Babayan A.F., Knyazev O.V. Adherence to therapy in patients with inflammatory bowel diseases. *Therapeutic archive.* 2018; 90 (12): 4–11 (in Russ.). DOI: 10.26442/00403660.2018.12.000001.
23. Jackson C.A., Clatworthy J., Robinson A., Horne R. Factors associated with non-adherence to oral medication for inflammatory bowel disease: a systematic review. *Am. J. Gastroenterol.* 2010; 105 (3): 525–539. DOI: 10.1038/ajg.2009.685.
24. Maev I.V., Kucheryavyy Yu.A., Andreev D.N. Modern approaches to antihelicobacter therapy optimization. *Lechaschi Vrach Journal.* 2014; 4: 73–79.
25. Kane S., Huo D., Aikens J., Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am. J. Med.* 2003; 114 (1): 39–43. DOI: 10.1016/s0002-9343(02)01383-9.
26. Khan N., Abbas A.M., Bazzano L.A., Koleva Y.N., Krousel-Wood M. Long-term oral mesalazine adherence and the risk of disease flare in ulcerative colitis: nationwide 10-year retrospective cohort from the veterans affairs healthcare system. *Aliment. Pharmacol. Ther.* 2012; 36 (8): 755–764. DOI: 10.1111/apt.12013.
27. Robinson A., Hankins M., Wiseman G., Jones M. Maintaining stable symptom control in inflammatory bowel disease: a retrospective analysis of adherence, medication switches and the risk of relapse. *Aliment. Pharmacol. Ther.* 2013; 38 (5): 531–538. DOI: 10.1111/apt.12396.
28. Nelidova A.V., Usacheva E.V., Zamakhina O.V., Suprun E.V. Influencing factors for adherence to treatment of patients with coronary atherosclerosis in the long term vascular events. *Modern Problems of Science and Education. Surgery*. 2015; 4: 354 (in Russ.).
29. Vasilenko A.G., Vasilenko Z.G., Nedochukova E.S., Smagina N.V., Popp V.Ya., Romza L.B., Efimov A.I., Levin M.Z., Efimov I.A. Analysis of causes of low adherence to the treatment of patients with inflammatory bowel diseases. *Bulletin of the Chelyabinsk Regional Clinical Hospital.* 2014; 3: 31–33 (in Russ.).
30. Kane S., Holderman W., Jacques P., Miodek T. Once daily versus conventional dosing of pH- dependent mesalamine long-term to maintain quiescent ulcerative colitis: Preliminary results from a randomized trial. *Patient Prefer Adherence*. 2008; 2: 253–258. DOI: 10.2147/PPA.S3698.
31. Ediger J.P., Walker J.R., Graff L., Lix L., Clara I., Rawsthorne P., Rogala L., Miller N., McPhail C., Deering K., Bernstein C.N. Predictors of medication adherence in inflammatory bowel disease. *Am. J. Gastroenterol.* 2007; 102 (7): 1417–1426. DOI: 10.1111/j.1572-0241.2007.01212.x.
32. Lachaine J. Medication adherence and persistence in the treatment of Canadian ulcerative colitis patients: analyses with the RAMQ database. *BMC Gastroenterol*. 2013; 13: 23. DOI: 10.1186/1471-230X-13-23.
33. Shapina M.V., Khalif I.L. Use of 5-aminosalicylic acid for treatment of ulcerative colitis in different dosage

modes. *Med. Counc. Remedium, Ltd.* 2017; 15: 44–50. DOI: 10.21518/2079-701x-2017-15-44-50.
34. Kane S.V., Cohen R.D., Aikens J.E., Hanauer S.B. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. *Am. J. Gastroenterol.* 2001; 96 (10): 2929–2933. DOI: 10.1111/J.1572-0241.2001.04683.X.
35. Krasner Ya.A., Osipenko M.F., Valuyskikh E.Yu., Rezakova M.V., Babich K.A. Frequency and features of non-alcoholic fatty liver disease steatohepatitis in patients with inflammatory bowel disease. *J. Sib. Med. Sci*. 2019; 3: 63–73. DOI: 10.31549/2542-1174-2019-3-63-73.
36. Selinger C., Robinson A., Leong R. Non-adherence to inflammatory bowel disease maintenance medication: extent and predictors. *J. Gastroenterol. Hepatol.* 2011; 26: 56–56.
37. Lopez A., Billioud V., Peyrin-Biroulet C., Peyrin-Biroulet L. Adherence to anti-TNF therapy in inflammatory bowel diseases: a systematic review. *Inflamm. Bowel Dis.* 2013; 19 (7): 1528–1533. DOI: 10.1097/MIB.0B013E31828132CB.
38. Alekseyeva O.P., Kasimova L.N., Goryacheva Y.Y. Treatment compliance of patients with gastro-intestinal diseases. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2016; 26 (1): 20–28 (in Russ.). DOI: 10.22416/1382-4376-2016-26-1-20-28.
39. Shale M.J., Riley S.A. Studies of compliance with delayed-release mesalazine therapy in patients with inflammatory bowel disease. *Aliment. Pharmacol. Ther.* 2003; 18 (2): 191–198. DOI: 10.1046/J.1365-2036.2003.01648.X.
40. Cervený P., Bortlík M., Kubena A., Vlcek J., Lakatos PL., Lukás M. Nonadherence in inflammatory bowel disease: results of factor analysis. *Inflamm. Bowel Dis.* 2007; 13 (10): 1244–1249. DOI: 10.1002/IBD.20189.
41. Mackner L.M., Crandall W.V. Oral medication adherence in pediatric inflammatory bowel disease. *Inflamm. Bowel Dis.* 2005; 11 (11): 1006–1112. DOI: 10.1097/01.MIB.0000186409.15392.54.
42. Gorjacheva E.E., Kitaeva I.I. Structure of anxiety disorders and treatment compliance of patients with functional gastrointestinal pathologies. *Neurological Bulletin.* 2015; 44 (2): 72–76 (in Russ.). DOI: 10.17816/NB13932.
43. Nalyotov A.V., Nalyotov S.V., Barinova A.S., Vunichenko Yu.S. The problem of compliance in current gastroenterology. *University clinic.* 2017; 13 (2): 213–218 (in Russ.).
44. Hommel K.A., Davis C.M., Baldassano R.N. Medication adherence and quality of life in pediatric inflammatory bowel disease. *J. Pediatr. Psychol.* 2008; 33 (8): 867–874. DOI: 1093/jpepsy/jsn022.
45. Horváth G., Farkas K., Hollósi R. Is there any association between impaired health-related quality of life and non-adherence to medical therapy in inflammatory bowel disease? *Scand. J. Gastroenterol.* 2012; 47 (11): 1298–303. DOI: 10.3109/00365521.2012.703233.
46. Perry J., Chen A., Kariyawasam V., Choong C., Teh W.L., Mitrev N., Kohler F., Leong R.W.L. Medication non-adherence in inflammatory bowel diseases is associated with disability. *Intest. Res.* 2018; 16 (4): 571–578. DOI: 10.5217/IR.2018.00033.
47. Sewitch M.J., Abrahamowicz M., Barkun A., Bitton A., Wild G.E., Cohen A., Dobkin PL. Patient nonadherence to medication in inflammatory bowel disease. *Am. J. Gastroenterol.* 2003; 98 (7): 1535–1544. DOI: 10.1111/J.1572-0241.2003.07522.X.
48. López San Román A., Bermejo F., Carrera E., Pérez-Abad M., Boixeda D. Adherence to treatment in inflammatory bowel disease. *Rev. Esp. Enferm. Dig.* 2005; 97 (4): 249–257. DOI: 10.4321/S1130-01082005000400005.
49. Ungaro R., Colombel J.-F., Lissoos T., Peyrin-Biroulet L. A treat-to-target update in ulcerative colitis: a systematic review. *Am. J. Gastroenterol.* 2019; 114 (6): 874–883. DOI: 10.14309/ajg.0000000000000183.
50. Agrawal M., Colombel J.-F. Treat-to-target in inflammatory bowel diseases, what is the target and how do we treat? *Gastrointest. Endosc. Clin. N. Am.* 2019; 29 (3): 421–436. DOI: 10.1016/j.giec.2019.02.004.
51. Knyazev O.V., Babayan A.F., Parfyonov A.I., Kagramanova A.V. Commitment to treatment of inflammatory bowel disease. *Medical alphabet.* 2019; 1 (6): 13–19 (in Russ.). DOI: 10.33667/2078-5631-2019-1-6(381)-13-18.
52. Drapkina O.M., Livzan M.A., Martynov A.I., Moiseev S.V., Nikolaev N.A., Skirdenko Yu.P. The first The First Russian consensus on the quantitative assessment of the adherence to treatment. *Medical News of the North Caucasus*. 2018; 13 (1-2): 259–271 (in Russ.). DOI: 10.14300/mnnc.2018.13039.
53. Shchukina B.O., Grigoryan V.V. Organization of specialized units – centers of IBD as a way of optimizing medical care for patients with ulcerative colitis and Crohn's disease. *Experimental and Clinical Gastroenterology.* 2017; 146 (10): 116–123 (in Russ.).
54. Choudhry N.K., Krumme A.A., Ercole P.M., Girdish C., Tong A.Y., Khan N.F., Brennan T.A., Matlin O.S., Shrank W.H., Franklin J.M. Effect of reminder devices on medication adherence: The REMIND randomized clinical trial. *JAMA Intern Med. American Medical Association*. 2017; 177 (5): 624–631. DOI: 10.1001/jamainternmed.2016.9627.
55. Tiao D.K., Jeganathan J., Chen A. Impact of targeted pharmacist counselling intervention on IBD medication adherence. *J. Gastroenterol. Hepatol.* 2014; 29: 106.
56. Fenerty S.D., West C., Davis S.A., Kaplan S.G., Feldman S.R. The effect of reminder systems on patients' adherence to treatment. *Patient Prefer Adherence.* 2012; 6: 127–35. DOI: 10.2147/PPA.S26314.

Authors contribution

Skirdenko Yu.P., Nikolaev N.A. – conception and design, final approval of the manuscript for publication. Gorbenko A.V., Andreev K.A., Fedorin M.M. – analysis and interpretation of data, final approval of the manuscript for publication. Livzan M.A., Bikbavova G.R. – critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication.

Authors information

Andreev Kirill A., Inspector, Department for the Development of Regional Healthcare and Medical Activity, Omsk State Medical University, Omsk, Russian Federation. ORCID 0000-0001-9976-573X.

Gorbenko Aleksandr V., Inspector, Department for the Development of Regional Healthcare and Medical Activity, Omsk State Medical University, Omsk, Russian Federation. ORCID 0000-0001-9703-9371.

Skirdenko Yulia P., Cand. Sci. (Med.), Assistant, Department of Internal Medicine and Gastroenterology, Omsk State Medical University, Omsk, Russian Federation. ORCID 0000-0002-6225-2444.

Nikolaev Nikolai A., Dr. Sci. (Med.), Associate Professor, Professor, Department of Internal Medicine and Gastroenterology, Vice-Rector for Medical Activity and Regional Healthcare, Omsk State Medical University, Omsk, Russian Federation. ORCID 0000-0002-3758-4930.

Livzan Maria A., Dr. Sci. (Med.), Professor, Head of the Department of Internal Medicine and Gastroenterology, Rector of Omsk State Medical University, Omsk, Russian Federation. ORCID 0000-0002-6581-7017.

Bikbavova Galiya R., Cand. Sci. (Med.), Associate Professor, Department of Internal Medicine and Endocrinology, Omsk State Medical University, Omsk, Russian Federation. ORCID 0000-0001-9252-9152.

Fedorin Maxim M., Inspector, Department for the Development of Regional Healthcare and Medical Activity, Omsk State Medical University, Omsk, Russian Federation. ORCID 0000-0002-0238-4664.

(✉) **Gorbenko Aleksander V.,** e-mail: prime.dr.alex@gmail.com

Received 14.08.2020
Accepted 28.12.2020