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Динамика клинических проявлений синдрома раздраженного кишечника на фоне приема ребамипида: промежуточные результаты исследования СОКРАТ

В.И. Симаненков, Н.В. Бакулина, А.С. Некрасова, Е.А. Елохина, Ю.Г. Топалова

Северо-Западный государственный медицинский университет им. И.И. Мечникова, Санкт-Петербург, Россия

Обоснование. Синдром раздраженного кишечника — одно из наиболее распространенных заболеваний желудочно-кишечного тракта. Его симптомы существенно снижают качество жизни больного. Из-за недостаточной эффективности современных способов лечения этого синдрома необходимо искать новые лекарственные препараты, фармакологическое действие которых направлено на патогенетические механизмы его формирования. В настоящее время все большее внимание уделяют влиянию синдрома повышенной эпителиальной проницаемости на раздраженный кишечник, в связи с чем перспективным является включение в комплексную терапию пациентов универсального цитопротектора ребамипида.

Цель работы — оценить влияние ребамипида на течение синдрома раздраженного кишечника.

Материалы и методы. В статье представлены промежуточные итоги исследования СОКРАТ в котором обследовали 40 больных синдромом раздраженного кишечника, разделенных на две группы, сопоставимые по полу, возрасту и типу заболевания. Пациенты основной группы (n = 21) получали дополнительно к стандартной спазмолитической терапии ребамипид, а пациенты группы сравнения (n = 19) — висмута трикалия дицитрат. Оценку гастроэнтерологических жалоб больных проводили до и после лечения при помощи опросников GSRS, 7×7, IBS-QOL и визуально-аналоговой шкалы.

Результаты. Оба препарата улучшили состояние пациентов, но более значимую положительную динамику простимулировал прием ребамипида, о чем свидетельствовало существенное уменьшение частоты и выраженности абдоминальных болей и симптомов, обусловленных констипацией, у пациентов основной группы.

Заключение. Исследование показало, что протективная активность ребамипида не только редуцирует симптомы, но и позитивно влияет на течение синдрома раздраженного кишечника.

Ключевые слова: синдром раздраженного кишечника; ребамипид; синдром повышенной эпителиальной проницаемости; цитопротектор.

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Dynamics of clinical manifestations of irritable bowel syndrome against the background of cytoprotector rebamipide intake: intermediate results of the SOKRAT program

Vladimir I. Simanenkov, Natalya V. Bakulina, Anna S. Nekrasova, Evgeniya A. Elokhina, Yuliya G. Topalova

North-West State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

BACKGROUND: Irritable bowel syndrome (IBS) is one of the most common diseases of the gastrointestinal tract, the detection rate of which in the general population is 9-23%, in the Russian Federation – 8.3-19%. IBS is the cause of chronic pain which accompanies patients throughout their life, significantly reducing its quality and disrupting social adaptation. Insufficient effectiveness of modern methods of treating IBS dictates the need to search for new drugs, the pharmacological action of which is aimed at the pathogenetic mechanisms of IBS formation. Currently, more and more attention in the development of IBS is paid to the syndrome of increased epithelial permeability, in connection with which it is promising to include the universal cytoprotector rebamipide in the complex therapy of patients with IBS.

AIM: To evaluate the effect of rebamipide on the course of irritable bowel syndrome.

MATERIALS AND METHODS: This article presents the intermediate results of the SOCRAT study, which has assessed the effect of rebamipide on the course of IBS. For this purpose, 40 patients with IBS have been examined and subsequently randomized into two groups comparable in gender, age and type of IBS. The patients of the main group (n = 21) received cytoprotector rebamipide in addition to standard antispasmodic therapy, and the patients of the comparison group (n = 19) received cytoprotector bismuth tripotassium dicitrate. Patients' gastroenterological complaints have been assessed before and after treatment using GSRS, 7x7, IBS-QOL questionnaires and a visual analogue scale.

RESULTS: According to the study findings, the well-being of the patients has improved in the both study groups. However, more significant positive dynamics has been observed in the main group, as evidenced by a significant decrease in the frequency and severity of abdominal pain and symptoms caused by constipation, which, in turn, led to an increase in the quality of life of the studied patients.

CONCLUSIONS: Thus, protective therapy of epithelium with rebamipide has not only a symptom-reducing effect, but also a positive effect on the course of IBS.

Keywords: irritable bowel syndrome; rebamipide; increased epithelial permeability syndrome; cytoprotector.

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ECO•VECTOR

BACKGROUND

Irritable bowel syndrome (IBS) is a gastrointestinal tract disease with a prevalence of 9%–23% in the global population and 8.3%–19% in the Russian population [1, 2]. Most patients with IBS are people of working age [3, 4] who had this disease for several years, which reduces significantly their quality of life [5] and disrupts social adaptation [6]. Existing methods of IBS therapy are effective in about half of the patients; thus, it becomes important to search for new therapeutic approaches [7].

According to the Rome IV Criteria and clinical guidelines, IBS is characterized by abdominal pain that occurs at least once a week, which is associated with defecation and changes in the frequency and/or shape of stools [8, 9]. IBS is caused by a combination of factors such as genetic predisposition [2, 10], dietary habits [11], previous acute intestinal infection [8, 10], previous antibiotic therapy [8, 10], psychoemotional stress [2, 7], dysbiotic disorders [7, 12], changes in the metabolic activity of the intestinal microflora [12], increased epithelial permeability syndrome [7, 13], development of low-activity inflammation in the intestines [4, 7], cytokine imbalance of the enteric immune system [14, 15], development of visceral hypersensitivity [16–18], motor–evacuation disorders [19], and changes in the neuroendocrine system (gut–brain axis) [20].

The study of IBS pathophysiology is currently focused on the syndrome of increased epithelial permeability [7, 13]. Impaired epithelial permeability of the mucous membrane indirectly leads to nonspecific low-activity inflammation in the intestinal wall, which results in visceral hypersensitivity and impaired motor activity of the intestine, which determine the development of the main symptoms of IBS [21]. The influence of increased epithelial permeability in IBS is indirectly evidenced by the low efficiency of contemporary treatment regimens, which lack drugs with cytoprotective properties. In the course of standard therapy, improvement in well-being is noted in 30% of the patients, and IBS passes into stable clinical remission only in 10% of the cases [10].

In the new pathogenetic approaches to IBS treatment, it is essential to strengthen the barrier function of the intestinal epithelium. IBS therapy is considered promising with the use of a universal drug rebamipide, and its protective activity is aimed at restoring the pre-epithelial, epithelial, and subepithelial levels of mucosal protection [13, 22, 23].

This study aimed to evaluate the changes in IBS clinical manifestations over time during the use of rebamipide as part of complex therapy.

MATERIALS AND METHODS

This study presents the interim results of SOCRAT (Syndrome of increased mucosal permeability in functional and organic diseases of the large intestine); a single-center open comparative randomized prospective study conducted at the Department of Internal Medicine, Clinical Pharmacology and Nephrology of the Mechnikov North Western State Medical University. It involved 40 patients with IBS, namely, men and women aged 18–70 years without decompensated somatic, acute infectious and oncological diseases, pregnancy, and lactation.

IBS was diagnosed based on a comprehensive laboratory and instrumental examination in accordance with the Rome IV Criteria [9]. The patients were distributed into two groups, comparable in terms of gender, age, and IBS type (Fig. 1). The main group (n = 21) received, in addition to standard antispasmodic therapy, the cytoprotector rebamipide, and the comparison group (n = 19) received bismuth tripotassium dicitrate, which also has pronounced cytoprotective properties and demonstrated its efficiency in the treatment of IBS in several studies [24–27].

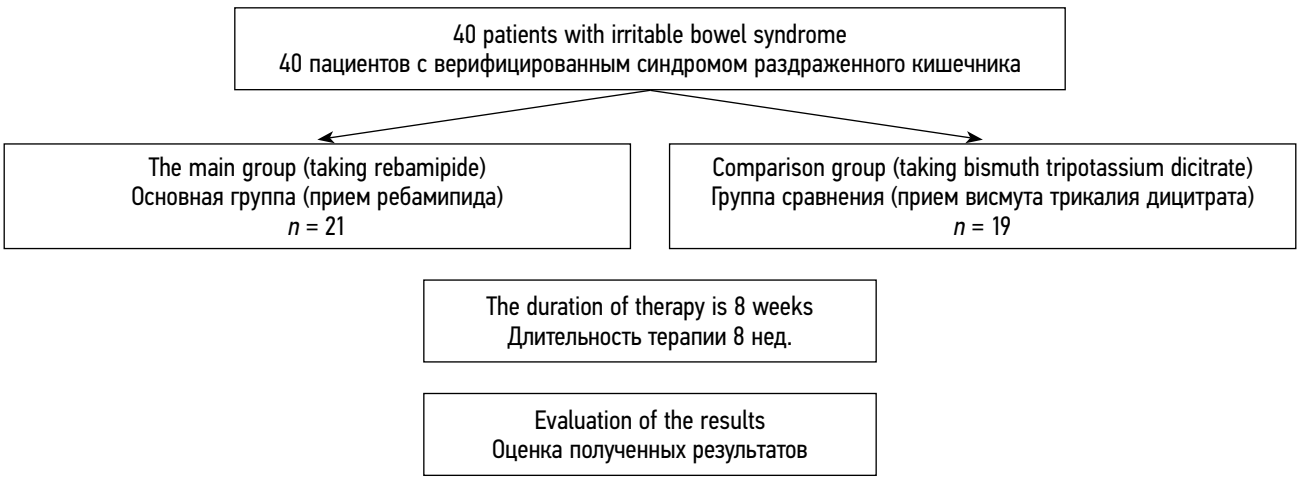

Fig. 1. Study design
Рис. 1. Дизайн исследования

1. In the past 4 weeks, how much have stomach pains been worrying you?
1. Насколько сильно за последние 4 нед. Вас беспокоили проблемы, связанные с болью в животе?

1	2	3	4	5	6	7	8	9	10

2. How badly have gastrointestinal diseases affected your daily life during the past 4 weeks?
2. Насколько сильно заболевания желудочно-кишечного тракта влияли на Вашу повседневную жизнь в течение последних 4 нед.?

1	2	3	4	5	6	7	8	9	10

Fig. 2. Visual analogue scales for assessing pain and the impact of gastrointestinal problems on the quality of life
Рис. 2. Визуально-аналоговые шкалы оценки выраженности болевого синдрома и влияния заболеваний желудочно-кишечного тракта на повседневную жизнь

To assess the therapeutic efficiency, the clinical manifestations of IBS were recorded using the Gastrointestinal Symptom Rating Scale (GSRS), 7 symptoms in 7 days (7 × 7), and Irritable Bowel Syndrome-Quality of Life (IBS-QOL). The GSRS questionnaire includes five subscales for measuring the severity of abdominal pain, reflux, diarrheal and dyspeptic syndromes, constipation, and summation of indicators. We used the 7 × 7 questionnaire to assess the dynamics of symptoms of functional dyspepsia and IBS, while IBS-QOL was used to assess the quality of life of patients with IBS. We also determined the pain syndrome severity and effect of gastrointestinal diseases on everyday life, using a visual analog scale (Fig. 2). The results were scored before and after treatment.

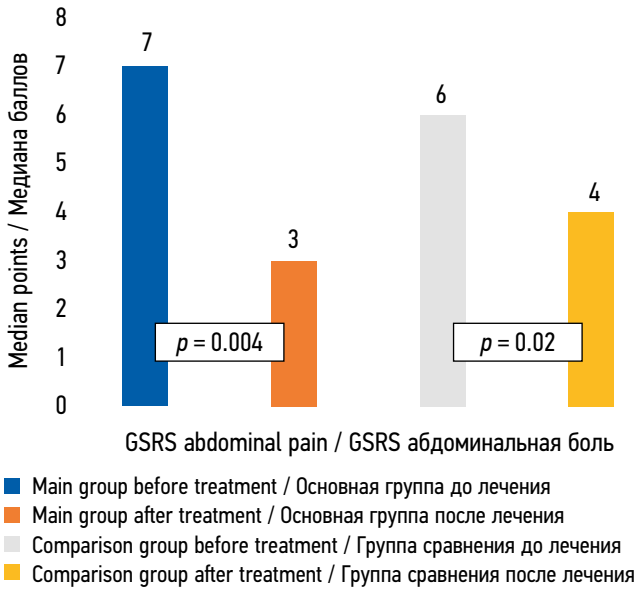

Fig. 3. Change in the score of abdominal pain relative to the baseline value during therapy (according to the abdominal pain subscale of the GSRS questionnaire)
Рис. 3. Изменение балла абдоминальной боли относительно исходного значения на фоне терапии (согласно подшкале измерения абдоминальной боли опросника GSRS)

During therapy, the patients were required to record the adverse events. After the therapy, one patient with low compliance withdrew from the main study group.

Statistica 10.0 software package was used for statistical data processing. Nonparametric statistical methods were used to assess the clinical manifestations using a scoring system. Data were presented as median, lower, and upper quartiles. The Wilcoxon test was used to analyze the associated variables. Differences between indicators were considered significant at $p < 0.05$. The mean age of the patients was 39.8 ± 13.8 years. There were 13 (32%) men and 27 (68%) women. IBS with severe constipation was recorded in 18 patients, severe diarrhea in 9, and a mixed form of IBS manifestations in 13.

RESULTS

Before the therapy, all patients were diagnosed with abdominal pain syndrome. After the treatment, positive changes were recorded in both groups. In the main group, the incidence and severity of abdominal pain decreased from 7 (5–8.5) to 3 (2.5–4) points according to the GSRS ($p = 0.004$) and from 6 (2–8) to 3.5 (2–5) points according to the visual analog scale ($p = 0.007$). In the comparison group, the intensity of abdominal pain decreased from 6 (5–8) to 4 (3–7) points ($p = 0.02$) according to the GSRS and from 6 (3–8) to 4 (2–8) points according to the visual analog scale ($p = 0.03$). Comparative analysis showed that the intensity of pain in the main group treated with rebamipide decreased more significantly than that in the comparison group ($p < 0.05$) (Fig. 3).

In the main group, the GSRS revealed a significant decrease in the frequency of constipation (i.e., incidence of constipation, feeling of incomplete emptying of the intestine during the previous week, and presence of hard stools) and a decrease in scores from 7.5 (4.5–10.5) to 5 (4–7.5) ($p = 0.02$). In the comparison group, this effect was not achieved ($p > 0.05$). All patients had the same tendency toward a decrease in the severity of reflux, diarrhea, and dyspeptic syndromes ($p > 0.05$).

In the analysis of the effect of treatment on the total GSRS score, a more significant positive trend was registered in the main group. In patients receiving rebamipide, this indicator decreased from 33 (28–41) to 24.5 (20–28) points ($p = 0.005$), and in the comparison group, it decreased from 32 (27–40) to 26.5 (21–30) points ($p = 0.02$) (Fig. 4). This finding is probably attributed to a more significant effect of treatment on the severity of abdominal pain and constipation in the main group.

According to the results of the 7 × 7 questionnaire, displaying the dynamics of the main symptoms of IBS and functional dyspepsia, the use of rebamipide led to a significant improvement in the well-being and a decrease in the total

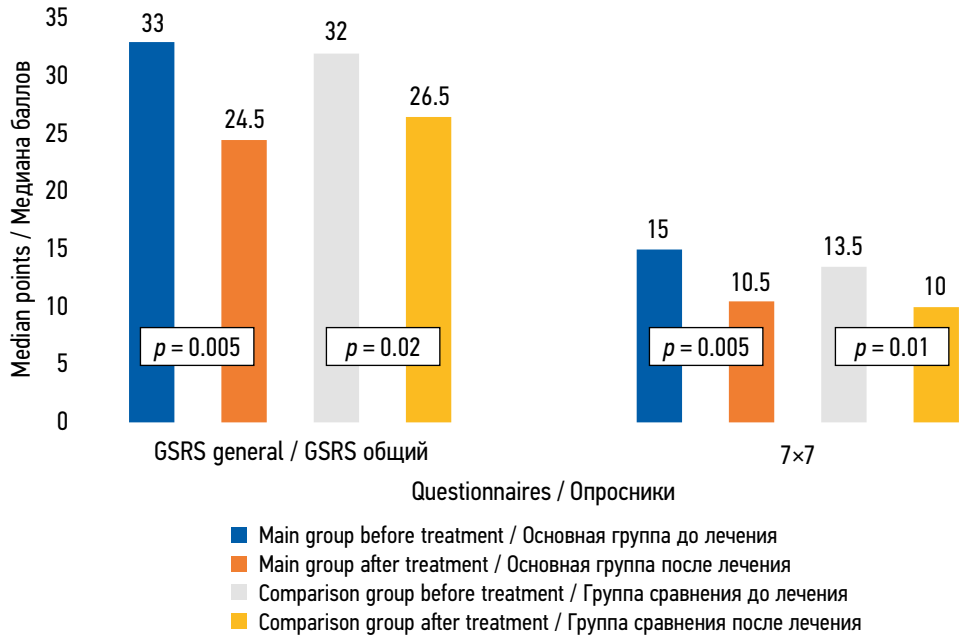

Fig. 4. Change in the total score of complaints relative to the baseline value during therapy (according to GSRS and 7x7 questionnaires)
Рис. 4. Изменение общей выраженности симптомов относительно исходного значения на фоне терапии (согласно опросникам GSRS и 7×7)

score from 15 (8–21) to 10.5 (3–17) points (p = 0.005) in the main group. In patients receiving bismuth tripotassium dicitrate, positive changes over time were less pronounced compared with those in the main group, that is, the mean score decreased from 13.5 (7–22) to 10 (4–16) (p = 0.01) (Fig. 5).

The improvement in the clinical course of IBS during treatment influenced the quality of life of the patients and was determined by the visual analog scale and IBS-QOL. Patients receiving rebamipide noted a significant decrease in the effect of gastrointestinal diseases on their daily life and a decrease in the median score of the visual analog scale from 6 (5–8) to 2 (2–3) (p = 0.007). In the comparison group, positive changes were less pronounced, and the median scores of the visual analog scale decreased from 6 (5–9) to 4 (2–7) points (p = 0.01). In the main group, the median IBS-QOL score decreased from 66.5 (60–92) to 50 (43–68) (p = 0.005), showing a significant improvement in the quality of life. In the comparison group, this indicator decreased from 70 (60–90) to 60 (45–76) (p = 0.02).

The study results demonstrate an increase in the efficiency of IBS treatment associated with the additional intake of rebamipide.

DISCUSSION OF RESULTS

Currently, the results of IBS treatment often remain unsatisfactory. The inclusion in the standard therapy of drugs that affect the pathogenetic mechanisms of IBS development can increase significantly the efficiency of treatment. The SOCRAT study revealed that the use of the universal cytoprotector rebamipide as part of the complex therapy of IBS led to an improvement in the well-being of the patients, as evidenced by a significant decrease in the frequency and severity of abdominal pain and constipation. The positive changes noted in patients have improved their quality of life.

The pharmacological effects of rebamipide are implemented through the induction of signaling pathways of kinases regulated by extracellular signals (ERK1 and ERK2), serine/threonine protein kinases B (Akt), c-Jun N-terminal

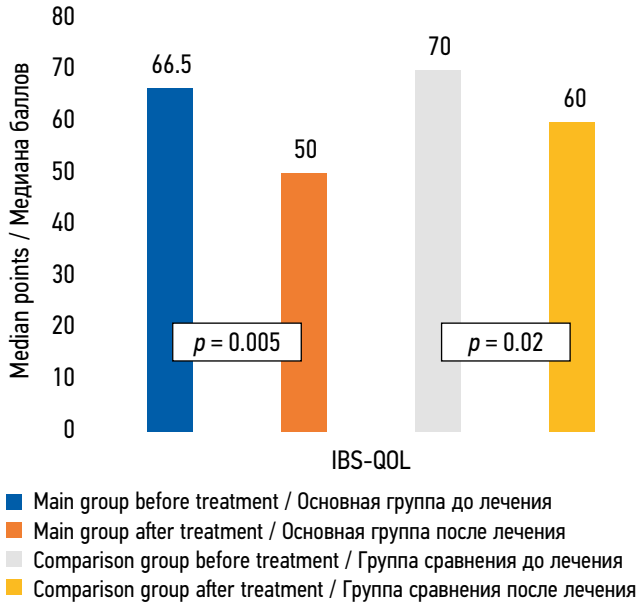

Fig. 5. Change in the total score of the quality of life relative to the baseline value during therapy (according to the IBS-QOL questionnaire)
Рис. 5. Изменение уровня качества жизни относительно исходного значения на фоне терапии (согласно опроснику IBS-QOL)

kinases, mitogen-activated protein kinases p38 (p38MAPK), and rapamycin kinase of mammals (mTOR). Their activation led to the formation of cyclooxygenase-2; subsequently, prostaglandins E2 (PGE2) increases [7, 28]. Under the influence of PGE2, the syntheses of glycoproteins and mucins increase, which contributes to the restoration of the structure and thickness of the mucous layer on the intestinal surface and provides a pre-epithelial level of protection [7, 13]. Increased production of PGE2 and prostacyclin (prostaglandin I2) under the influence of rebamipide contributes to the neutralization of free radicals, inhibition of neutrophil activation, decrease in the synthesis of proinflammatory cytokines [29, 30], and stimulation of angiogenesis [28], while reducing low-level inflammation and causing a subepithelial level of protection [7, 15]. In addition, increased production of cytoprotective prostaglandins leads to a change in the permeability of the gastrointestinal mucosa by increasing the expression of proteins zonula occludens 1 and claudins, which form tight junctions of epithelial cells [31], thereby increasing the stability of the epithelial protection layer [7, 13].

Rebamipide has a complex effect on the gastrointestinal mucosa, restoring pre-epithelial, epithelial, and subepithelial levels of protection and correcting the increased epithelial permeability of the intestinal mucosa [7]. The effect of increased epithelial permeability and the versatility of rebamipide determine its clinical efficacy in patients with IBS and pathogenetically justify its inclusion in the complex therapy.

CONCLUSIONS

1. In the treatment of IBS, rebamipide decreases the severity of the pain syndrome, reduces constipation, and increases the patient's quality of life.
2. Rebamipide not only eliminates the symptoms but also affects positively the course of IBS.
3. Compared with bismuth tripotassium dicitrate, rebamipide is more effective for the treatment of IBS.

ADDITIONAL INFORMATION

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REFERENCES

1. Aziz I, Palsson OS, Törnblom H, et al. The Prevalence and impact of overlapping rome IV-diagnosed functional gastrointestinal disorders on somatization, quality of life, and healthcare utilization: a cross-sectional general population study in three countries. *Am J Gastroenterol.* 2018;113(1):86–96. DOI: 10.1038/ajg.2017.421

2. Ambulatornaya gastroenterologiya. Rukovodstvo dlya vrachej. Ed. by I.G. Bakulin. Moscow; 2020. (In Russ.)

3. Ardatskaya MD, Topchy TB, Loschinina YuN, Kalashnikova MA. Clinical efficiency of butyric acid and inulin in rapid relief of pain syndrome in patients with irritable bowel syndrome. *Lechaschi Vrach.* 2015;(12):79–86. (In Russ.)

4. Pushkina AV, Avalueva EB, Vorobiev SL. Immunohistochemical characteristics of the colonic mucosa in patients with irritable bowel syndrome. *Gastroenterology of St. Petersburg.* 2020;(3–4):3–12. (In Russ.)

5. El Serag HB, Olden K, Bjorkman D. Healthrelated quality of life among persons with irritable bowel syndrome: a systematic review. *Aliment Pharmacol Ther.* 2002;16(6):1171–1185. DOI: 10.1046/j.1365-2036.2002.01290.x

6. Baranovsky AYu, Wasserman LI, Fedorova VL, Chugunov DN. Irritable bowel syndrome: clinical, psychological and psychosocial interdependence. *Experimental and Clinical Gastroenterology*. 2019;(12(172)):3. (In Russ.). DOI: 10.31146/1682-8658-ecg-172-12-34-39

7. Simanenkov VI, Maev IV, Tkacheva ON, et al. Syndrome of increased epithelial permeability in clinical practice. Multidisciplinary national Consensus. *Cardiovascular Therapy and Prevention.* 2021;20(1):121–278. (In Russ.). DOI: 10.15829/1728-8800-2021-2758

8. Klinicheskie rekomendacii. Sindrom razdrazhennogo kishechnika. 2021–2023 [Internet]. *Minzdrav RF.* Available from: https://legalacts.ru/doc/klinicheskie-rekomendatsii-sindrom-razdrazhennogo-kishechnika-utv-minzdravom-rossii/. Accessed: Sep 15, 2021. (In Russ.)

9. Sheptulin A, Vize-Khripunova MA. Review of Rome-IV criteria for the irritable bowel syndrome: are there any basic changes? *Russian Journal of Gastroenterology, Hepatology, Coloproctology.* 2016;26(5):99–103. (In Russ.). DOI: 10.22416/1382-4376-2016-26-5-99-103

10. Ivashkin VT, Shelygin YA, Baranskaya EK, et al. Clinical recommendations of the Russian Gastroenterological Association and the Association of Coloproctologists of Russia for the diagnosis and treatment of irritable bowel syndrome. *Russian Journal of Gastroenterology, Hepatology, Coloproctology.* 2017;27(5):76–93. (In Russ.). DOI: 10.22416/1382-4376-2017-27-5-76-93

11. Barbalho SM, Goulart RA, Araújo AC, et al. Iirritable bowel syndrome: a review of the general aspects and the potential role of vitamin D. *Expert Rev Gastroenterol Hepatol.* 2019;13(4):345–359. DOI: 10.1080/17474124.2019.1570137

12. Ivashkin VT, Zolnikova OYu. Irritable bowel syndrome in terms of changes in the microbiota. *Russian Journal of Gastroenterology, Hepatology, Coloproctology.* 2019;29(1):84–92. (In Russ.). DOI: 10.22416/1382-4376-2019-29-1-84-92

13. Andreev DN. The role of alterations in permeability of the intestinal mucosa in the genesis of functional gastrointestinal disorders. *Consilium Medicum.* 2019;21(8):29–34. (In Russ.). DOI: 10.26442/20751753.2019.8.190539

14. Casado-Bedmar M, Keita AV. Potential neuro-immune therapeutic targets in irritable bowel syndrome. *Therap Adv Gastroenterol.* 2020;13:1756284820910630. DOI: 10.1177/1756284820910630

15. Choghakhori R, Abbasnezhad A, Hasanvand A, Amani R. Inflammatory cytokines and oxidative stress biomarkers in irritable bowel syndrome: Association with digestive symptoms and quality of life. *Cytokine.* 2017;93:34–43. DOI: 10.1016/j.cyto.2017.05.005

16. Farzaei MH, Bahramsoltani R, Abdollahi M, Rahimi R. The role of visceral hypersensitivity in irritable bowel syndrome: pharma-

cological targets and novel treatments. *Neurogastroenterol Motil.* 2016;22(4):558–574. DOI: 10.5056/jnm16001

17. Farré R, Vanheel H, Vanuytsel T, et al. In functional dyspepsia, hypersensitivity to postprandial distention correlateswwith meal-related symptom severity. *Gastroenterology.* 2013;145(3):566–573. DOI: 10.1053/j.gastro.2013.05.018

18. Ludidi S, Mujagic Z, Jonkers D, et al. Markers for visceral hypersensitivity in patients with irritable bowel syndrome. *Neurogastroenterol Motil.* 2014;26(8):1104–1111. DOI: 10.1111/nmo.12365

19. Kanazawa M, Palsson OS, Thiwan SM, et al. contributions of pain sensitivity and colonic motility to IBS symptom severity and predominant bowel habits. *Am J Gastroenterol.* 2008;103(10):2550–2561. DOI: 10.1111/j.1572-0241.2008.02066.x

20. Coss-Adame E, Rao SS. Brain and gut interactions in irritable bowel syndrome: new paradigms and new understandings. *Curr Gastroenterol Rep.* 2014;16(4):379. DOI: 10.1007/s11894-014-0379-z

21. Johansso MEV, Sjövall H, Hansson GC. The gastrointestinal mucus system in health and disease. *Nat Rev Gastroenterol Hepatol.* 2013;10(6):352–361. DOI: 10.1038/nrgastro.2013.35

22. Simanenkov VI, Lutaenko EA, Nikogosyan AA. Clinical and pharmacological characteristics of rebamipide in deseases of the gastrointestinal tract. *Medical Council.* 2016;(19):88–95. (In Russ.). DOI: 10.21518/2079-701X-2016-19-88-95

23. Simanenkov VI, Tikhonov SV. Rebamipide: new opportunities for gastroenteroprotection. *Therapeutic Archive.* 2015;87(12):134–137. (In Russ.). DOI: 10.17116/terarkh20158712134-137

24. Punkina AV, Avalueva EB, Ellinidi VN, et al. Optimizatsiya nekotorykh pokazateley lokal'nogo immuniteta patsientov s sindromom razrazhennogo kishechnika pri lechenii preparatom vismuta. *Gastroenterologiya Sankt-Peterburga.* 2016;(1–2):11–14. (In Russ.)

25. Punkina AV, Avalueva EB, Danilova IA, et al. Ispol'zovanie preparatov vismuta trikaliya ditsitrata v lechenii sindroma razdrazhennogo kishechnika s preobladaniem diarei. *Lechashchiy vrach.* 2016;6:81–84. (In Russ.)

26. Simanenkov VI, Bakulina NV, Tikhonov SV. Bismuth tripotassium dicitrat: from pharmaceutical characteristics to clinical efficacy. *Medical Alphabet.* 2019;1(6(381)):23–28. (In Russ.). DOI: 10.33667/2078-5631-2019-1-6(381)-23-28

27. Tkachenko EI, Avalueva EB, Sitkin SI, et al. Ispol'zovanie preparatov vismuta v lechenii sindroma razdrazhennogo kishechnika. *Gastroenterologiya Sankt-Peterburga.* 2013;(3–4):11–14. (In Russ.)

28. Tarnawski AS, Chai J, Pai R, Chiou SK. Rebamipide activates genes encoding angiogenic growth factors and Cox2 and stimulates angiogenesis: a key to its ulcer healing action? *Dig Dis Sci.* 2004;49(2):202–209. DOI: 10.1023/b:ddas.0000017439.60943.5c

29. Arakawa T, Kobayashi K, Yoshikawa T, Tarnawski A. Rebamipide: overview of its mechanisms of action and efficacy in mucosal protection and ulcer healing. *Dig Dis Sci.* 1998;43(9):5–13.

30. Nishizawa T, Suzuki H, Nakagawa I, et al. Rebamipide - promoted restoration of gastric mucosal sonic hedgehog expression after early Helicobacter pylori eradication. *Digestion.* 2009;79(4):259–262. DOI: 10.1159/000213241

31. Suzuki T, Yoshida N, Nakabe N, et al. Prophylactic effect of rebamipide on aspirin-induced gastric lesions and disruption of tight junctional protein zonula occludens-1 distribution. *J Pharmacol Sci.* 2008;106(3):469–477. DOI: 10.1254/jphs.fp0071422

СПИСОК ЛИТЕРАТУРЫ

1. Aziz I., Palsson O.S., Törnblom H. et al. The prevalence and impact of overlapping rome IV-diagnosed functional gastrointestinal disorders on somatization, quality of life, and healthcare utilization: a cross-sectional general population study in three countries // Am. J. Gastroenterol. 2018. Vol. 113, No. 1. P. 86–96. DOI: 10.1038/ajg.2017.421

2. Амбулаторная гастроэнтерология: руководство для врачей / под ред. И.Г. Бакулина. М., 2020.

3. Ардатская М.Д., Топчий Т.Б., Лощинина Ю.Н., Калашникова М.А. Клиническая эффективность масляной кислоты и инулина в купировании болевого синдрома у пациентов с синдромом раздраженной кишки // Лечащий врач. 2015. № 12. С. 79–86.

4. Пушкина А.В., Авалуева Е.Б., Воробьев С.Л. Иммуногистохимические характеристики слизистой оболочки толстой кишки у пациентов с синдромом раздраженного кишечника // Гастроэнтерология Санкт-Петербурга. 2020. № 3–4. С. 3–12.

5. El Serag H.B., Olden K., Bjorkman D. Healthrelated quality of life among persons with irritable bowel syndrome: a systematic review // Aliment. Pharmacol. Ther. 2002. Vol. 16, No. 6. P. 1171–1185. DOI: 10.1046/j.1365-2036.2002.01290.x

6. Барановский А.Ю., Вассерман Л.И., Федорова В.Л., Чугунов Д.Н. Синдром раздраженной кишки: клинико-психологические и психосоциальные соотношения // Экспериментальная и клиническая гастроэнтерология. 2019. № 12(172). С. 34–39. DOI: 10.31146/1682-8658-ecg-172-12-34-39

7. Симаненков В.И., Маев И.В., Ткачева О.Н. и др. Синдром повышенной эпителиальной проницаемости в клинической практике. Мультидисциплинарный национальный консенсус // Кардиоваскулярная терапия и профилактика. 2021. Т. 20, № 1. С. 121–278. DOI: 10.15829/1728-8800-2021-2758

8. Клинические рекомендации. Синдром раздраженного кишечника. 2021–2023 [Электронный ресурс] // Минздрав РФ. Режим доступа: https://legalacts.ru/doc/klinicheskie-rekomendatsii-sindrom-razdrazhennogo-kishechnika-utv-minzdravom-rossii/. Дата обращения: 15.09.2021.

9. Шептулин А.А., Визе-Хрипунова М.А. Римские критерии синдрома раздраженного кишечника IV пересмотра: есть ли принципиальные изменения? // Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2016. Т. 26, № 5. С. 99–103. DOI: 10.22416/1382-4376-2016-26-5-99-103

10. Ивашкин В.Т., Шелыгин Ю.А., Баранская Е.К. и др. Клинические рекомендации Российской гастроэнтерологической ассоциации и Ассоциации колопроктологов России по диагностике и лечению синдрома раздраженного кишечника // Российский журнал гастроэнтерологии, гепатологии и колопроктологии. 2017. Т. 27, № 5. С. 76–93. DOI: 10.22416/1382-4376-2017-27-5-76-93

11. Barbalho S.M., Goulart R.A., Araújo A.C. et al. Iirritable bowel syndrome: a review of the general aspects and the potential role of vitamin D // Expert. Rev. Gastroenterol. Hepatol. 2019. Vol. 13, No. 4. P. 345–359. DOI: 10.1080/17474124.2019.1570137

12. Ивашкин В.Т., Зольникова О.Ю. Синдром раздраженного кишечника с позиций изменений микробиоты // Российский журнал гастроэнтерологии, гепатологии и колопроктологии. 2019. Т. 29, № 1. С. 84–92. DOI: 10.22416/1382-4376-2019-29-1-84-92

13. Андреев Д.Н. Роль нарушения проницаемости слизистой оболочки кишечника в генезе функциональных заболеваний желудочно-кишечного тракта // Consilium Medicum. 2019. Т. 21, № 8. С. 29–34. DOI: 10.26442/20751753.2019.8.190539
14. Casado-Bedmar M., Keita A.V. Potential neuro-immune therapeutic targets in irritable bowel syndrome // Therap. Adv. Gastroenterol. 2020. Vol. 13. P. 1756284820910630. DOI: 10.1177/1756284820910630
15. Choghakhori R., Abbasnezhad A., Hasanvand A., Amani R. Inflammatory cytokines and oxidative stress biomarkers in irritable bowel syndrome: Association with digestive symptoms and quality of life // Cytokine. 2017. Vol. 93. P. 34–43. DOI: 10.1016/j.cyto.2017.05.005
16. Farzaei M.H., Bahramsoltani R., Abdollahi M., Rahimi R. The role of visceral hypersensitivity in irritable bowel syndrome: pharmacological targets and novel treatments // Neurogastroenterol. Motil. 2016. Vol. 22, No. 4. P. 558–574. DOI: 10.5056/jnm16001
17. Farré R., Vanheel H., Vanuytsel T. et al. In functional dyspepsia, hypersensitivity to postprandial distention correlateswwith mealrelated symptom severity // Gastroenterology. 2013. Vol. 145, No. 3. P. 566–573. DOI: 10.1053/j.gastro.2013.05.018
18. Ludidi S., Mujagic Z., Jonkers D. et al. Markers for visceral hypersensitivity in patients with irritable bowel syndrome // Neurogastroenterol. Motil. 2014. Vol. 26, No. 8. P. 1104–1111. DOI: 10.1111/nmo.12365
19. Kanazawa M., Palsson O.S., Thiwan S.M. et al. contributions of pain sensitivity and colonic motility to IBS symptom severity and predominant bowel habits // Am. J. Gastroenterol. 2008. Vol. 103, No. 10. P. 2550–2561. DOI: 10.1111/j.1572-0241.2008.02066.x
20. Coss-Adame E., Rao S.S. Brain and gut interactions in irritable bowel syndrome: new paradigms and new understandings // Curr. Gastroenterol. Rep. 2014. Vol. 16, No. 4. P. 379. DOI: 10.1007/s11894-014-0379-z
21. Johansson M.E.V., Sjövall H., Hansson G.C. The gastrointestinal mucus system in health and disease // Nat. Rev. Gastroenterol. Hepatol. 2013. Vol. 10, No. 6. P. 352–361. DOI: 10.1038/nrgastro.2013.35
22. Симаненков В.И., Лутаенко Е.А., Никогосян А.А. Клинико-фармакологические особенности применения ребамипида при заболеваниях желудочно-кишечного тракта // Медицинский совет. 2016. № 19. С. 88–95. DOI: 10.21518/2079-701X-2016-19-88-95
23. Симаненков В.И., Тихонов С.В. Ребамипид — новые возможности гастроэнтеропротекции // Терапевтический архив. 2015. Т. 87, № 12. С.134–137. DOI: 10.17116/terarkh20158712134-137
24. Пушкина А.В., Авалуева Е.Б., Эллиниди В.Н. и др. Оптимизация некоторых показателей локального иммунитета пациентов с синдромом раздраженного кишечника при лечении препаратом висмута // Гастроэнтерология Санкт-Петербурга. 2016. № 1–2. С. 11–14.
25. Пушкина А.В., Авалуева Е.Б., Данилова И.А. и др. Использование препарата висмута трикалия дицитрата в лечении синдрома раздраженного кишечника с преобладанием диареи // Лечащий врач. 2016. № 6. С. 81–84.
26. Симаненков В.И., Бакулина Н.В., Тихонов С.В. Препараты висмута трикалия дицитрата: от фармацевтических характеристик к клинической эффективности // Медицинский алфавит. 2019. Т. 1, № 6(381). С. 23–28. DOI: 10.33667/2078-5631-2019-1-6(381)-23-28
27. Ткаченко Е.И., Авалуева Е.Б., Ситкин С.И. и др. Использование препаратов висмута в лечении синдрома раздраженного кишечника // Гастроэнтерология Санкт-Петербурга. 2013. № 3–4. С. 11–14.
28. Tarnawski A.S., Chai J., Pai R., Chiou S.K. Rebamipide activates genes encoding angiogenic growth factors and Cox2 and stimulates angiogenesis: a key to its ulcer healing action? // Dig. Dis. Sci. 2004. Vol. 49, No. 2. P. 202–209. DOI: 10.1023/b:ddas.0000017439.60943.5c
29. Arakawa T., Kobayashi K., Yoshikawa T., Tarnawski A. Rebamipide: overview of its mechanisms of action and efficacy in mucosal protection and ulcer healing // Dig. Dis. Sci. 1998. Vol. 43, No. 9. P. 5–13.
30. Nishizawa T., Suzuki H., Nakagawa I. et al. Rebamipide-promoted restoration of gastric mucosal sonic hedgehog expression after early Helicobacter pylori eradication // Digestion. 2009. Vol. 79, No. 4. P. 259–262. DOI: 10.1159/000213241
31. Suzuki T., Yoshida N., Nakabe N. et al. Prophylactic effect of rebamipide on aspirin-induced gastric lesions and disruption of tight junctional protein zonula occludens-1 distribution // J. Pharmacol. Sci. 2008. Vol. 106, No. 3. P. 469–477. DOI: 10.1254/jphs.fp0071422

AUTHORS INFO

Vladimir I. Simanenkov, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-1956-0070;
eLibrary SPIN: 8073-2401; e-mail: visimanenkov@mail.ru

Natalya V. Bakulina, MD, Dr. Sci. (Med.);
ORCID: https://orcid.org/0000-0003-4075-4096;
Scopus Author ID: 7201739080; ResearcherID: N-7299-2014;
eLibrary SPIN: 9503-8950; e-mail: nv_bakulina@mail.ru

*** Anna S. Nekrasova**, MD, Cand. Sci. (Med.);
address: 41 Kirochnaya St., Saint Petersburg, 191015, Russia;
eLibrary SPIN: 7502-5036; e-mail: annanekrasova@list.ru

Evgeniya A. Elokhina;
e-mail: kopiuti1995@gmail.com

Yuliya G. Topalova;
ORCID: https://orcid.org/0000-0003-3999-6848;
eLibrary SPIN: 1301-6443; e-mail: topalova.julias@yandex.ru

ОБ АВТОРАХ

Владимир Ильич Симаненков, д-р мед. наук, профессор;
ORCID: https://orcid.org/0000-0002-1956-0070;
eLibrary SPIN: 8073-2401; e-mail: visimanenkov@mail.ru

Наталья Валерьевна Бакулина, д-р мед. наук;
ORCID: https://orcid.org/0000-0003-4075-4096;
Scopus Author ID: 7201739080; ResearcherID: N-7299-2014;
eLibrary SPIN: 9503-8950; e-mail: nv_bakulina@mail.ru

*** Анна Сергеевна Некрасова**, канд. мед. наук;
адрес: Россия, 191015, Санкт-Петербург, ул. Кирочная, д. 41;
eLibrary SPIN: 7502-5036; e-mail: annanekrasova@list.ru

Евгения Алексеевна Елохина;
e-mail: kopiuti1995@gmail.com

Юлия Геннадьевна Топалова;
ORCID: https://orcid.org/0000-0003-3999-6848;
eLibrary SPIN: 1301-6443; e-mail: topalova.julias@yandex.ru

* Corresponding author / Автор, ответственный за переписку