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Rebamipide during chronic gastritis: *H. pylori* eradication therapy and restoration of gastric mucosa barrier function

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Aim: to present evidence justifying prescription of rebamipide during chronic gastritis.
Key points. Experimental and clinical studies have demonstrated that rebamipide increases concentration of prostaglandins (prostaglandin E2 and prostacyclin) and production of mucin, manages inflammation and oxidative stress, controls apoptosis and autophagy. Pleiotropic effects of rebamipide are aimed at restoration of epithelium barrier function and can be implemented during chronic gastritis for various indications. When added to the *H. pylori* eradication therapy, rebamipide increases its effectiveness and tolerability. During atrophic gastritis, long-term treatment with rebamipide has resulted in reduction of degree of atrophy and intestinal metaplasia. Effectiveness of rebamipide during erosive gastritis, for treatment and prevention of stomach and duodenum disorders associated with nonsteroidal anti-inflammatory drugs is proven. Rebamipide manages symptoms of dyspepsia during chronic gastritis and during functional dyspepsia.
Conclusion. Prescription of rebamipide during chronic gastritis for various indications is proved from the perspective of evidence-based medicine during *H. pylori* eradication therapy and for restoration of mucosa barrier function.
Keywords: chronic gastritis, *Helicobacter pylori,* rebamipide, *H. pylori* eradication therapy, erosive gastritis, dyspepsia
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Ребамипид при хроническом гастрите: эрадикационная терапия *H. pylori* и восстановление барьерной функции слизистой оболочки желудка

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Цель исследования: представить доказательные данные обоснования назначения ребамипида при хроническом гастрите.
Основные положения. В экспериментальных и клинических исследованиях показано, что ребамипид повышает концентрацию простагландинов (простагландина Е2 и простациклина) и продукцию муцина, купирует воспаление и оксидативный стресс, регулирует апоптоз и аутофагию. Плейотропные эффекты ребамипида направлены на восстановление барьерной функции эпителия и могут быть реализованы при хроническом гастрите по разным показаниям. Ребамипид при добавлении к эрадикационной терапии *H. pylori* повышает ее эффективность и переносимость. При атрофическом гастрите длительное лечение ребамипидом привело к снижению степени атрофии и кишечной метаплазии. Доказана эффективность ребамипида при эрозивном гастрите, для лечения и профилактики поражения желудка и двенадцатиперстной кишки, ассоциированных с нестероидными противовоспалительными препаратами. Ребамипид купирует симптомы диспепсии при хроническом гастрите и при функциональной диспепсии.
Заключение. Назначение ребамипида при хроническом гастрите по разным показаниям обосновано с позиции доказательной медицины при эрадикационной терапии *H. pylori* и для восстановления барьерной функции слизистой оболочки.
Ключевые слова: хронический гастрит, *Helicobacter pylori*, ребамипид, эрадикационная терапия *H. pylori*, эрозивный гастрит, диспепсия
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Introduction

The diagnosis of chronic gastritis is one of the most frequent in clinical practice. For example, in Moscow in 2022 in the digestive system primary morbidity structure diagnoses gastritis and duodenitis (K29) accounted for 16.5 % (230.2 cases for 100.000 of population). The disease remains very relevant despite of decrease in cases of newly diagnosed gastritis in Moscow (in the last five years by almost 1.5 times) [1].

High frequency of gastritis is conditioned by widespread of *H. pylori* infection in Russian Federation. Despite of distinct tendency of decreasing share of *H. pylori*-positive persons in the population, frequency of infection on the average amounts to 38.8 %, and the highest indicators are documented in the age group of 41–50 years old — 43.9 % [2].

Aims of eradication of the *H. pylori* infection are presented in the Clinical guidelines of Russian Gastroenterological Association on Diagnosis and treatment of gastritis and duodenitis [3]. The therapy problem that remains is patients care after successful eradication of the *H. pylori* infection, including with atrophic gastritis (severe atrophy and/or intestinal metaplasia in the body and in the antrum — OLGA/OLGIM III/IV) and in patients with a family history of stomach cancer [4, 5]. Risk of stomach cancer occurrence in this group of patients continues to persist and based on medication approaches to prevention need further examination.

According to instruction, indication of prescription of rebamipide (Rebagit) are gastric ulcer, chronic gastritis with gastric hyperacidity in the acute stage, erosive gastritis and prevention of mucosa disorders occurrences on the background of nonsteroidal anti-inflammatory drugs (NSAID) administration. Thus, in the Clinical guidelines of Russian Gastroenterological Association on Diagnosis and treatment of gastritis and duodenitis, prescription of rebamipide is presented in various clinical settings, which will be discussed further [3].

Purpose of the review of references is to present evidence justifying prescription of rebamipide during chronic gastritis.

Rebamipide mechanism of action

Biological effects of rebamipide, such as cytoprotection, healing of damages, and elimination of inflammation are implemented in various tissues, in not only the gastrointestinal mucosa and specifically the stomach [6]. Rebamipide increases concentration of prostaglandins (prostaglandin E2 and prostacyclin) and production of mucin, removes oxygen free radicals, and manages inflammation [6–8].

Anti-inflammatory and antioxidative effects were demonstrated in the clinical studies in cases of gastritis and gastric ulcer with prescription of rebamipide together with eradication therapy of *H. pylori* or after its completion [9, 10]. In the study of K.B. Hahm et al., eradication of *H. pylori* in a group with rebamipide was not only higher, but both mucosal malondialdehyde levels and myeloperoxidase activity were significantly lower. Levels of IL-1, IL-6, IL-8 and TNF-α cytokines in mucosa as well as GRO-α (neutrophils activating factor) and RANTES (chemokines released by T-cells upon activation) became significantly lower after treatment of *H. pylori*, especially in the group receiving rebamipide. Thus, addition of rebamipide to the *H. pylori* eradication protocols had both quantitative and qualitative advantages: the eradication effectiveness was increasing together with decreasing of oxidative stress and levels of bound by the *H. pylori*-associated gastritis proinflammatory cytokines [10].

A series of experimental studies has shown that rebamipide provides protective effect on gastric mucosa under action of NSAID (indomethacin) not only because of anti-inflammatory action by inhibition of the NF-κB signal pathway and management of oxidative stress, by also because of controlling the apoptosis. Under action of NSAID, the expression of genes responsible for apoptosis is increasing in the gastric cells, and rebamipide inhibits these genes [11].

New mechanisms of rebamipide action for restoration of epithelial barrier were uncovered in an experiment with ethanol-induced gastric damage. Autophagy is a natural mechanism due to which cell disposes of damaged proteins and organelles, provides protective action on cells “survivability” in case of chemical injury. Autophagy processes are closely adjoined with endoplasmic reticulum stress phenomena. In the experiment, ethanol has been activating the endoplasmic reticulum stress and inducing apoptosis (control group laboratory animals 15.24 ± 1.10 %; group under the influence of ethanol 33.80 ± 1.47 %, $p < 0.001$) under conditions of autophagy inhibition. Rebamipide has been reducing the rate of apoptosis (20.78 ± 1.63 %) and significantly improving endoplasmic reticulum stress indicators and related signal pathway NF-κB. Thus, it was proven that rebamipide activates autophagy, crucial process of maintaining the barrier function of gastrointestinal tract [12].

Rebamipide during the *H. pylori* infection eradication therapy

Eradication therapy of *H. pylori* has fundamental significance during chronic gastritis as etiotropic treatment and measure to prevent progression of mucous membrane atrophic changes [3, 13]. Thus,

selection of the most efficient anti-Helicobacter therapy protocol has essential importance. In the Clinical guidelines of Russian Gastroenterological Association on Diagnosis and treatment of gastritis and duodenitis, addition of rebamipide to the eradication protocols was considered appropriate as a measure to improve the efficacy of anti-Helicobacter treatment [3]. This recommendation is justified by data of three meta-analyses.

In the meta-analysis of T. Nishizawa et al., percentage of the *H. pylori* eradication with prescription of rebamipide amounted to 73.3 %, and without it — 61.4 %, odds ratio (OR) amounted to 1.74 (95 % confidence interval (CI: 1.19–2.53) [14]. In the meta-analysis of D.A. Andreev et al. of 2019, which included 11 studies (n = 1227), achieved OR was 1.753 (95 % CI: 1.312–2.333; $p < 0.001$) in favor of the prescription of rebamipide [15]. Meta-analysis of D.A. Andreev et al. of 2022, has analyzed studies conducted in Russian Federation using rebamipide made by PRO.MED.CS. company. In the 6 controlled studies (n = 531) generalized eradication effectiveness was 90.376 % (95 % CI: 86.311–93.560) in patients who received rebamipide, and 81.681 % (95 % CI: 76.499–86.141) in patients without rebamipide. Addition of rebamipide to the *H. pylori* eradication protocols positively increases treatment effectiveness (OR — 2.162, 95 % CI: 1.268–3.685; $p = 0.005$). In the group taking rebamipide, a decrease in the incidence of adverse events at the border of statistical significance is observed (OR — 0.569; 95 % CI: 0.333–0.970; $p = 0.038$) [16].

Rebamipide has no influence on the viability of *H. pylori* bacteria. However, with preliminary addition of rebamipide to the epithelial cells culture, adhesion of *H. pylori* strains obtained from patients with chronic gastritis and gastric ulcer to MKN-28 and MKN-45 cells was significantly suppressed. Rebamipide inhibits adhesion of not only *H. pylori*, but also *E. coli.* The authors made an assumption that *H. pylori* may survive in the mucin after beginning of eradication therapy and reengage with epithelial surface. Thus, rebamipide prevents recolonization of *H. pylori* and, because of sufficiently long antibiotic treatment together with the rebamipide; eradication effectiveness can be increased [17].

Considering the rebamipide effect on the *H. pylori* infection, it should be mentioned a number of special studies dedicated to the bacteria virulence factor to the cytotoxin-associated protein A (CagA), the oncoprotein of bacterial origin. The CagA interaction with the gastric epithelium cells results in dysregulation of a number of signaling pathways: MAPK, PI3K/Akt, NF-κB, Wnt/β-catenin, JAK-STAT, and Hippo. The consequence of this is an induction of inflammation and pathologic changes in the structure, polarity, and proliferation of epitheliocytes, which is considered as an important stage of carcinogenesis [18]. Rebamipide has been suppressing CagA-induced expression of phospholipase D1 (PLD1) by means of inhibition of the NF-κB binding to the promoter PLD1, as well as inhibiting of the PLD activity. In addition, rebamipide has been suppressing the *H. pylori*-induced expression of the matrix metalloproteinase-9 and IL-8. These results prove that rebamipide can support anti-tumoral effect by inhibiting of signal pathway CagA-NF-κB-PLD1 [19]. In the study of K.H. Lee et al., rebamipide has been protecting epithelial cells against CagA-induced effects, at that not only inhibiting of NF-κB and reducing production of IL-8, but also has normalized condition of intercellular contacts (zonula occludens) [20]. D.W. Kang et al. have demonstrated the chemo protective potential of rebamipide against carcinogenic influence of CagA because of suppression of β-catenin and its target [21].

Rebamipide effect on inflammation, atrophy and intestinal metaplasia during chronic gastritis

For the potentiation of gastric mucosa protective properties, Clinical guidelines of Russian Gastroenterological Association on Diagnosis and treatment of gastritis and duodenitis recommend treatment with bismuthate tripotassium dicitrate or rebamipide for 4–8 weeks [3].

During analysis of this provision in the Clinical guidelines, it is advisable to reveal the significance of the increased epithelial permeability syndrome during gastritis [22, 23]. Increased epithelial permeability syndrome is coupled with the inflammatory process in the gastric mucosa and serves as the typical pathophysiologic mechanism during gastritis and functional dyspepsia. *H. pylori* makes a decisive contribution in the occurrence of this syndrome adversely affecting the pre-epithelial, epithelial and post-epithelial levels of the mucosa protection. Thus, the increased epithelial permeability syndrome takes part in the gastritis pathogenesis and maintaining of the chronic inflammation, and drug therapy having cytoprotective effect is pathogenically justified [22, 23]. We can assume that restoration of gastric epithelial barrier may have an important value for prevention of stomach cancer in persons with atrophic gastritis and intestinal metaplasia after eradication of the *H. pylori* infection.

Effectiveness of rebamipide is proven in improvement of the inflammation histological indicators in patients with gastritis even without eradication of *H. pylori*. K. Haruma et al. have studied 86 patients infected with *H. pylori*: 53 were taking 300 mg of rebamipide per day for 12 months and 33 patients were a control group. In the rebamipide group significant decrease of mononuclear infiltration in the antrum (from 1.42 ± 0.15 to 1.02 ± 0.15; $p < 0.01$) and stomach body (from 1.60 ± 0.15 to 1.21 ± 0.14; $p < 0.05$) was observed. Neutrophils infiltration was also reduced in the antrum (from 0.98 ± 0.14 to 0.70 ± 0.13; $p < 0.05$), which was related to decrease in production of inducible NO-synthase. In the serum

of rebamipide taking patients a marked decline in the gastrin content (from 276.3 ± 58.3 pg/mL to 173.0 ± 34.2 pg/mL; $p < 0.05$) was observed, whereas in the control group no changes were observed [24].

In the controlled randomized trial of T. Kamada et al., 169 patients with proven successful eradication of *H. pylori* were divided into group taking 300 mg of rebamipide per day for 12 months and a group without treatment. Histopathological examination of the gastric biopsies was conducted during including in the trial and in 1 year according to the Sydney system. Gastritis and atrophy activity indicators have improved in both groups without distinction between groups, which was explained by the authors because of eradication of the *H. pylori* infection. Notably that chronic inflammation of the small curvature of the stomach body significantly improved in the rebamipide group in comparison with group without treatment (1.12 ± 0.08 vs. 1.35 ± 0.08; $p = 0.043$) [25].

Evidences are accumulating on the intrinsic positive effect of rebamipide on atrophy and intestinal metaplasia. In the trial aimed at assessment of precancerous changes of gastric mucosa during gastritis on the background of therapy with rebamipide for 26 weeks, endoscopic examination with assessment of mucosa condition according to modified Lanza scale, histopathological examination of the gastric biopsies according to the Sydney system and immunohistochemical examination with of intestinal metaplasia markers, transcription factor CDX2 (caudal type homeobox transcription factor 2) and trefoil factor 3 (TFF3) were carried out. Treatment with rebamipide contributed to improvement mucosa condition by Lanza scale, decrease in inflammation, degree of intestinal metaplasia and low-grade malignant intraepithelial neoplasia. On the background rebamipide treatment, the percentage of cells expressing CDX2 (31.5 % vs. 15.7 %, $p = 0.021$) and TFF3 (44.9 % vs. 25.8 %, $p = 0.012$) has been decreased [26].

The randomized trial covered 53 patients after endoscopic mucosal resection or mucosectomy with dissection in the submucosal layer for gastric mucosal dysplasia or early gastric cancer. It is obvious that for this group of patients monitoring of the gastric mucosa condition has fundamental significance for prevention of metachronous cancer. The trial included *H. pylori*-negative patients, and on *H. pylori*-positive patients, eradication therapy was performed. Thirty-four patients received rebamipide in the dosage of 300 mg per day for a year, and 19 patients received placebo. Degree of atrophy in antrum has positively improved after treatment with rebamipide (1.870 ± 0.932 before treatment / 1.430 ± 0.986 after treatment; $p = 0.013$), degree of intestinal metaplasia in the antrum has also improved (1.750 ± 0.963 before treatment / 1.370 ± 1.032 after treatment; $p = 0.038$) [27].

The large-scale follow-up study observed patients after endoscopic mucosectomy with dissection in the submucosal layer, made in 2011–2014. During 73,416 person years of observation, 711 patients were again diagnosed with stomach cancer, including 377 patients taking low doses (below median line) of rebamipide and 334 persons – high doses (above median line) of rebamipide (37157.4 and 36258.3 per 100.000 person years, respectively); logarithmic ranking test, $p = 0.052$). After correction for such factors as age, gender, diagnosis at the moment of endoscopic resection performance, application of high doses of rebamipide was associated with reducing of the risk of stomach cancer (risks ratio – 0.858; 95 % CI: 0.739–0.995; $p = 0.043$) [28]. For this group of patients at high risk of neoplasm, rebamipide has been named as a gastric cancer chemo preventive agent [28].

Rebamipide with erosive gastritis

Clinical guidelines of Russian Gastroenterological Association for patients with erosive gastritis and duodenitis, including on the background of taking of nonsteroidal anti-inflammatory drugs, in order to achieve healing of erosions, recommend performing treatment with PPI for 4–6 weeks and/or rebamipide for 4–8 weeks [3]. Effectiveness of rebamipide with erosive gastritis has been proven in controlled randomized trials [29, 30].

Meta-analysis dedicated to the effectiveness of rebamipide for prevention and treatment of NSAID-induced gastropathy and enteropathy has covered 15 trials ($n = 965$). It was shown that with short terms of NSAID rebamipide is more efficient than placebo for healing of stomach and duodenum disorders. The studies have demonstrated as much effectiveness in comparison with PPI, H2-receptor blockers and misoprostol. In comparison with placebo, rebamipide is efficient during NSAID-induced enteropathy (relative risk – 2.70; 954 % CI: 1.02–7.16; $p = 0.045$) [31]. Since rebamipide is the only drug in the Russian Federation having evidential basis for this kind of indication, conclusion on the rebamipide effectiveness for prevention and treatment of NSAID-induced enteropathy has fundamental importance.

Balance of PPI and rebamipide for care of patients that need a long-term treatment with NSAID is presented in study together with assessment of gastrointestinal mucosa condition with esophagogastroduodenoscopy and capsular video image endoscopy. Patients with rheumatoid arthritis, osteoarthritis, Strümpell – Marie disease on the background of meloxicam therapy were prescribed with rebamipide or lansoprazole (control group) for 12 weeks. As the starting point of efficiency evaluation occurrence of gastric ulcer was selected, which has not developed in a single patient. Difference in number of erosions and small bowel ulcer before inclusion into trial and with control trial on the background of rebamipide amounted to 0.6 ± 3.06; and on the background of PPI was 1.33 ± 4.71. Fraction of patients with small bowel erosive disorder after 12 weeks of treatment

was 20 % in the rebamipide group and 40 % in the PPI group [32].

Thus, rebamipide is efficient in care of patients with erosive gastritis and provides protective effect in case of NSAID administration not only in the stomach but in other sections of gastrointestinal tract as well.

Rebamipide and dyspepsia

A number of cited above trials of rebamipide have shown improvement in clinical performance [25, 26].

For the patients with chronic gastritis and symptoms of dyspepsia, Clinical guidelines of Russian Gastroenterological Association on Diagnosis and treatment of gastritis and duodenitis, recommend treatment with rebamipide both as sole therapy and as a part of muilimodality therapy [3].

Since it is based on the conclusions of meta-analysis, this recommendation corresponds to the credibility level A and confidence level 1. Data of 17 trials with total number of 2,170 patients (1,224 – with rebamipide, 946 – placebo / control) were reviewed: in 12 trials a rebamipide effect with organic dyspepsia (ulcer disease, reflux esophagitis, NSAID-induced gastropathy), in 5 trials with functional dyspepsia has been examined. Rebamipide significantly managed symptoms of dyspepsia, relative risk of 0.77, 95 % CI: 0.64 to 0.93; standardized mean difference -0.46; 95 % CI: from -0.83 to -0.09). Thus, rebamipide manages symptoms of dyspepsia during organic disorders and during functional dyspepsia [33].

Conclusion

Rebamipide (Rebagit) is recommended for a wide range of indications in chronic gastritis: as part of *H.pylori* eradication therapy; to reduce histological manifestations of gastritis such as inflammation, atrophy and intestinal metaplasia; for the treatment and prevention of erosive gastritis; to manage symptoms of dyspepsia during gastritis and functional dyspepsia. Proven effects on increase in the prostaglandin concentration, mucin production, reducing inflammation and oxidative stress, control of apoptosis and autophagy make rebamipide (Rebagit) a universal signaling molecule that activates mechanisms for maintaining the integrity of the epithelial barrier. Further controlled studies, including those in different regions of the Russian Federation, are urgently needed for precision evaluation of the effects of this promising drug in chronic gastritis, including cancer prevention.

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