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Advisable including glucosaminylmuramyldipeptide in *Helicobacter pylori* therapy: experience of ten-year investigation

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Abstract. *Helicobacter pylori* infection is a common bacterial infection in humans and is associated with peptic ulcer disease and chronic gastritis. The presence of natural resistance to some antibiotics in bacteria, as well as the appearance of primary and secondary resistance to antibacterial agents, complicates treatment and determines the search for new methods of therapy. The aim of this study was to evaluate the efficacy and safety of 10-year complex treatment of patients with duodenal ulcer associated with *H.pylori*, 136 patients (96 men, 40 women; mean age 45.8 ± 14.8 years; 18–65 years). *H.pylori* was determined morphologically and by rapid urease test one day before the start of therapy, after 1, 6, 12 months, 2 years, 5 and 10 years. Patients of the first group received basic therapy: omeprazole 0.02 g 2 times a day, clarithromycin 0.5 g 2 times a day, amoxicillin 1 g 2 times a day, for 10 days (OCA group 1; n = 98). Patients of the second group, in addition to the basic therapy, took 1 mg per day drug Licopid (group 2 OCAL; n = 38). At the 1st stage of the clinical study, 130 patients completed eradication therapy. Tracking completeness was 96 %. The frequency of *H.pylori* eradication after per protocol treatment: OCA – 83 % (95 % CI: 75 %–91 %), OCAL – 97 % (95 % confidence interval (CI): 92 %–100 %). The incidence of adverse reactions after treatment (per protocol): OCA – 26 % (95 % CI: 17–35 %; nausea; n = 24), discontinued treatment – 5 % (95 % CI: 0.8 %–10 %; diarrhea; n = 5); OCAL – 3 % (95 % CI: 0.01 %–8 %; nausea; n = 1), all were treated. Taking the drug Licopid 1 mg (glucosaminyl muramyl dipeptide, JSC Peptek, Russia) as part of complex therapy contributed to the elimination of *H.pylori* and the absence of relapses for 2 years. Observation of patients in the next 5 and 10 years also showed the advantage of including the immunomodulator in therapy: a significant 15 % decrease in *H.pylori* reinfection (P <0.05), a 23 % decrease in the frequency of gastrointestinal adverse reactions (P<0.01), compared with a 10-day standard triple regimen without immunomodulatory therapy with glucosaminylmuramyl dipeptide. When using several antibiotics in *H.pylori* eradication therapy, not only pathogenic, but also commensal microorganisms are destroyed, the waste products of which are vital and maintain immune homeostasis, including through the NOD2 receptors of innate immunity. The effectiveness of the complex therapy of *H.pylori* infection can be explained by the fact that the drug Licopid compensates for the signal for innate immunity receptors that is missing due to the absence of commensals, providing an adequate immune response and preventing chronicity and recurrence of infection.

Key words: duodenal ulcer, Helicobacter pylori, Licopid, glucosaminyl muramyl dipeptide, eradication, recurrence, reinfection, immunomodulatory therapy

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Целесообразность включения глюкозаминилмурамилдипептида в терапию *Helicobacter pylori*: опыт десятилетнего наблюдения

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Аннотация. Инфекция *Helicobacter pylori* относится к распространенным бактериальным инфекциям человека и ассоциирована с язвенной болезнью и хроническим гастритом. Наличие у бактерии природной резистентности к некоторым антибиотикам, а также появление первичной и вторичной устойчивости к антибактериальным средствам осложняет лечение и обуславливает поиск новых способов терапии. Целью настоящего исследования явилась оценка эффективности и безопасности 10-летнего комплексного лечения 136 пациентов с язвой двенадцатиперстной кишки. Для идентификации *H.pylori* в двух группах использовали быстрый уреазный тест и морфологические исследования. Эндоскопическое обследование проводили за один день до начала терапии, через 1, 6, 12 месяцев, 2 года, 5 и 10 лет. Пациенты первой группы принимали базисную терапию: дважды в сутки омепразол по 0,02 г, кларитромицин 0,5 г 2 раза в сутки, амоксициллин 1 г 2 раза в сутки, в течение 10 дней (1 группа ОКА; n=98). Пациенты второй группы в дополнение к базисной терапии в течение 10 дней принимали 1мг в день препарат Ликопид (2 группа ОКАЛ; n=38). На 1-ом этапе клинического исследования закончили эрадикационную терапию 130 пациентов. Полнота отслеживания составила 96 %. Частота эрадикации *H.pylori* после лечения per protocol: ОКА – 83 % (95 % ДИ: 75 %-91 %), ОКАЛ – 97 % (95 % доверительный интервал (ДИ): 92 %-100 %). Частота развития побочных реакций после лечения (per protocol): ОКА – 26 % (95 % ДИ: 17-35 %; тошнота; n=24), прекратили лечение – 5 % (95 % ДИ: 0,8 %-10 %; диарея; n=5); ОКАЛ – 3 % (95 % ДИ: 0,01 %-8 %; тошнота; n=1), все прошли лечение. Прием препарата Ликопид 1 мг (глюкозаминилмурамилдипептид, АО Пептек, Россия) в составе комплексной терапии способствовал элиминации *H.pylori* и отсутствию рецидивов в течение 2 лет. Наблюдение за пациентами в последующие 5 и 10 лет также показало преимущество включения иммуномодулятора в терапию: достоверное снижение на 15 % реинфекции *H.pylori* (P<0,05), снижение частоты побочных реакций со стороны ЖКТ на 23 % (P<0,01), по сравнению с 10-ти дневной стандартной тройной схемой без иммуномодулирующей терапии глюкозаминилмурамилдипептидом. При использовании нескольких антибиотиков в эрадикационной терапии *H.pylori* уничтожаются не только патогенные, но и комменсальные микроорганизмы, продукты жизнедеятельности которых являются жизненно необходимыми и поддерживают иммунный гомеостаз, в том числе через NOD2 рецепторы врожденного иммунитета. Эффективность

комплексной терапии инфекции *H.pylori* может быть объяснена тем, что препарат Ликопид компенсирует недостающий в связи с отсутствием комменсалов сигнал для рецепторов врожденного иммунитета, обеспечивая адекватный иммунный ответ и препятствуя хронизации и рецидивированию инфекции.

Ключевые слова: язва двенадцатиперстной кишки, *Helicobacter pylori*, ликопид, глюкозаминилмурамилдипептид, эрадикация, рецидив, реинфекция, иммуномодулирующая терапия

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Since the identification of *Helicobacter pylori* in 1982, and much has been learned about this bacterium, it remains one of the most common bacterial infection in humans [1- 4]. The bacterium causes a diverse pathology of the upper gastrointestinal tract from *H.pylori*-induced gastroduodenitis and *H.pylori*-associated dyspepsia to gastroduodenal ulcer, MALT lymphoma and gastric cancer. This requires appropriate anti- Helicobacter therapy [2, 5]. *H.pylori* eradication is a first-line therapy for *H.pylori*-infected patients with dyspepsia (Kyoto Global Consensus on *Helicobacter pylori*; Regulation 9). *H.pylori*-infected patients should be offered eradication therapy unless otherwise stated (Kyoto Global Consensus on *Helicobacter pylori*; Regulation 17) [5]. Eradication of bacteria is also necessary to control complications and reduce the number of relapses of gastroduodenal ulcer associated with *H.pylori* infection. The clinical effect of successful *H.pylori* eradication is manifested by a sharp drop in the recurrence rate of this disease after elimination of the bacterium [6].

The presence of natural resistance to some antibiotics in bacteria, as well as the appearance of primary and secondary resistance to antibacterial agents, complicates treatment and determines the search for new methods of therapy. This is reflected in current international guidelines for *H.pylori* eradication, which presents not only the first-line treatment regimens, but also various other treatment regimens taking into account the clarithromycin-resistant *H.pylori* strains in the region (Table 1).

Table 1

Recommended regimens for eradication of *Helicobacter pylori* (Consensus Ma-Astricht V, 2017) [2]

Standard triple therapy: **PPI + clarithromycin + amoxicillin (10—14 days)**
Standard quadrotherapy with bismuth: **PPI + tetracycline + metronidazole + de-nol (10—14 days)**
Sequential therapy: **5—7 days — PPI + amoxicillin, then 5—7 days — PPI + clarithromycin + metronidazole / tinidazole**
Concomitant therapy or quadrotherapy without bismuth: **PPI + amoxicillin + clarithromycin + metronidazole / tinidazole (10—14 days)**
Hybrid therapy: **PPI + amoxicillin 14 days + from 8 to 14 days — clarithromycin + metronidazole / tinidazole**
First line starting circuits: **standard triple therapy, standard bismuth quadrotherapy**

Note: PPI is a proton pump inhibitor.

Таблица 1

Рекомендуемые схемы для эрадикации *Helicobacter pylori* (Консенсус Маастрихт V, 2017 г.) [2]

Стандартная тройная терапия: **ИПП + кларитромицин + амоксициллин (10—14 дней)**
Стандартная квадротерапия с висмутом: **ИПП + тетрациклин + метронидазол + Де-нол (10—14 дней)**
Последовательная терапия: **5—7 дней — ИПП + амоксициллин, затем 5—7 дней — ИПП + кларитромицин + метронидазол/тинидазол**
Сопутствующая терапия или квадротерапия без висмута**: ИПП + амоксициллин + кларитромицин + метронидазол/тинидазол (10—14 дней)**
Гибридная терапия: **ИПП + амоксициллин 14 дней + с 8 по 14 день — кларитромицин + метронидазол/тинидазол**
Стартовые схемы первой линии: **стандартная тройная терапия, стандартная квадротерапия с висмутом**

Quadrotherapy for the CIS countries

Quadrotherapy for the CIS countries (taking into account the growth of *H.pylori* resistance to antibiotics and the presence of fast metabolizers (60-70 %) in the population of the Russian Federation; Megraud Francis "Approaches to the treatment and diagnosis of *H.pylori*. European Register data" 2015) includes Omeprazole 0.02 g x 3 times a day, Amoxicillin 1.0 g x 3 times a day, Josamycin 1.0 g x 2 times a day, De-nol 0.24 g x 2 times a day. The duration of therapy is 10-14 days.

Measures to increase the effectiveness of standard triple therapy taking into account the growth of *H.pylori* resistance to antibiotics (Recommendations of the Russian Gastroenterological Association, 2018): Omeprazole 0.04 g x 2 times a day, Clarithromycin 0.5 g x 2 once a day, Amoxicillin 1.0 g x 2 times a day, De-nol 0.24 g x 2 times a day. The duration of therapy is 10-14 days. Addition to the standard triple therapy of probiotic strains of *Bifidobacterium* and *Lactobacillus* [7].

It is very difficult to reach *H.pylori* eradication. In most patients, a year after successful eradication, reinfection of *H.pylori* occurs within the next 10 years [8, 9]. In the Russian Federation and countries of Eastern Europe, *H.pylori* reinfection exceeds 5 % per year, in Western Europe and the USA - less than 3 % per year [3, 10]. In order to optimize standard therapy different approaches are investigated, for example the usage of probiotics [2, 11, 12].

This is reflected in Provisions 9 and 10 of the Consensus of Maastricht V [2], which are formulated as follows: certain probiotics are effective in reducing gastrointestinal side effects caused by *H.pylori* eradication therapy. Specific strains should only be selected on the basis of proven clinical efficacy (Consensus Maastricht V; Regulation 9). Certain probiotics may have a beneficial effect on *H.pylori* eradication (Consensus Maastricht V; Regulation 10). It is believed that probiotic strains, in particular *Lactobacillus*, decrease the activity of bacterial urease, the motility of *H.pylori* and the adhesion of *H.pylori* to gastric epithelial cells [7].

The concept is formulated that the immunomodulating effect plays a significant role in the mechanism of antimicrobial action of pro-biotics [13]. The origin of the immunomodulator and its influence on the mucosa are the main issues [14, 15]. It is known that glucosaminyl muramyl dipeptide (GMDP) modulate immune answer via NOD2 receptors and YB1 protein [16, 17] and is effective in the therapy of infections [18-20], allergy[21, 22], psoriasis [23], correction of cytopenia [24] and microbiocenosis [25]. The positive effect of Licopid 10mg on the elimination of *H.pylori* was investigated earlier [26, 27] correlates with another dosage of this drug – 1mg.

During the first stage of this randomized prospective comparative clinical study of the effectiveness of *H. pylori* elimination in standart triple therapy with addition of GMDP 1mg was carried out. During the second stage of this investigation the frequency of relapse and reinfection of *Helicobacter pylori* was measured.

Material and methods

This study was approved by the Ethics Committee of the Vitebsk State Medical University (Vitebsk, Belarus) and was carried out during 2000-2020 years. Prior to the start of the study, informed consent was obtained from all patients to participate in the study and the processing of personal data.

The first stage of a prospective, randomized, comparative clinical study was conducted to evaluate the efficacy and safety of *H.pylori* eradication during standard triple therapy with Licopid.

Inclusion criteria: the presence of *H.pylori*- associated duodenal ulcer (DU).

Exclusion criteria: patients using antibacterial drugs less than a month before the start of eradication therapy or FEGDS research.

Eradication therapy was performed in 136 patients (96 men, 40 women; mean age 45.8 ± 14.8 years (mean ± SD; 18 - 65 years) with a duodenal ulcer associated with *H. pylori* (Table 2). Patients were divided by a randomized lottery drum method into 2 groups according to treatment protocols: omeprazole 0.04 g / day, clarithromycin 1 g / day, amoxicillin 2 g / day for 10 days (OCA; n = 98); omeprazole 0.04 g / day, clarithromycin 1 g / day, amoxicillin 2 g / day, Lycopid 0.001 g / day for 10 days (OCAL; n = 38).

Table 2

Patient profile

Treatment Protocols	Number of Patients	Gender m	f	Age (years)	Disease duration (years)
Omeprazole 0.04 g / day Clarithromycin 1 g / day Amoxicillin 2 g / day	98	69	29	48,3 + 14,2	8,7 + 3,9
Omeprazole 0.04 g / day Clarithromycin 1 g / day Amoxicillin 2 g / day Lycopid 0.001 g / day	38	27	11	37,2 + 14,3	8,3 + 3,9
Total	136	96	40	45,8 + 14,8	8,6 + 4,1

Таблица 2

Характеристика пациентов

Протоколы лечения	Количество пациентов	Пол муж	жен	Возраст (годы)	Длительность заболевания (годы)
Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут	98	69	29	48,3 + 14,2	8,7 + 3,9
Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут Ликопид 0,001 г/сут	38	27	11	37,2 + 14,3	8,3 + 3,9
Всего	136	96	40	45,8 + 14,8	8,6 + 4,1

The study completed 130 patients. Six people (4.4 %) were excluded from the general group (5 people from the OCA group and 1 person from the OCAL group) due to the lack of data on the diagnosis of *H.pylori* or the cessation of medication. The completeness of tracking was 95.6 %.

In the second stage were included 113 patients aged from 18 till 65 which successfully passed first stage (44.1 ± 13.5 years, 81 men and 32 women).

Over 10 years, 11 people (9.7 %; 95 % CI: 4.2-15.2 %) were excluded from the general group due to the refusal of repeated endoscopic examinations

with the diagnosis of *H.pylori* (8 people) or on their own desire (3 people). The completeness of tracking up to 2 years was 108 (95.6 %; 95 % CI: 91.8-99.4 %) people, from 2 to 5 years old - 104 (92.0 %; 95 % CI: 87.0 -97.0 %) of a person, from 6 to 10 years old - 102 (90.3 %; 95 % CI: 84.8-95.8 %) of a person.

In a randomized trial 113 patients had the following treatment: 0.04 g omeprazole, 1.0 g clarithromycin, 2.0 g amoxicillin per day dyring 10 days (group OCA ; n=77). patients from the the second group received 0.04 g omeprazole, 1.0 g clarithromycin, 2.0 g amoxicillin and 0.001 g Lycopid per day (group OCAL ; n = 36).

The tissue investigation of the duodenum was carried out by standard systematization and methods [28, 29]. To identify areas of gastric metaplasia (GM) of duodenum, an additional staining of histological sections of the mucous membrane of duodenal ulcer was performed with Chic -alcian blue (Serva) pH 1.0 and 2.5 [30].

Intestinal metaplasia and all cell- and tissue-morphologic characteristics were assessed using a visual analogue scale [31-33] according to the histological section of the Houston modification of the Sydney classification.

During the histological examination of the duodenal mucosa standard indicators were taken into account [30, 34]. Diagnostics of *H.pylori* was carried out by Romanovsky-Giemsa stain; assessment using a standard visual-analogue scale [35] and a quick urease test (standard test systems Jatrox®-Hp-Test, Rohm Pharma, Germany; HELPIL® and AMA RUT Pro®, LLC “AMA”, Russia) [36].

For statistical processing the program «STATISTICA 10.0» and t-test were used. If the distribution of the variable was not normal, the Shapiro-Wilk test was used. The Mann-Whitney U-test was used to evaluate the differences between two independent small samples by the level of the trait, measured quantitatively. Patient age was presented as mean ± standard deviation (SD). P levels <0.05 were considered significant [37].

Results and its discussion

The results of the first stage of a prospective, randomized, comparative clinical study are represented in the Table 3.

The frequency of *H.pylori* eradication depending on the prescribed treatment (ITT) and the actual treatment received (PP): OCA - 78.6 % (95 % CI: 70.4 % -86.8 %) and 82.8 % (95 % CI: 75.1 % -90.5 %), OCAL - 94.7 % (95 % CI: 87.5 % -100 %) and 97.3 % (95 % CI: 91.7 % -100 %) respectively. The incidence of adverse reactions (PR) depending on the prescribed treatment and the actual treatment received: OCA - 24.5 % (95 % CI: 15.9 % -33.1 %) and 25.8 % (95 % CI: 16, 8-34.8 %; nausea; n = 24), discontinued treatment - 5.1 % (95 % CI: 0.7 % -9.5 %) and 5.4 % (95 % CI: 0.8 % -10.0 %; diarrhea; n = 5); OCAL - 2.6 % (95 % CI: 0.01 % -7.7 %) and 2.7 % (95 % CI: 0.01 % -7.8 %; nausea; n = 1), discontinued treatment - 0 %.

Reception of Lycopid 0.001 g / day during a 10-day three-component anti-bacterial treatment significantly increased *H.pylori* eradication by 16.0 % (according to ITT) and 14.5 % (according to PP; respectively $\chi2 = 3.87$; $P = 0.0492$ and $\chi2 = 4.0$; $P = 0.0455$), with a significant decrease in PR frequency by 2.5 % (according to ITT) and 2.7 % (according to PP; respectively, $\chi2 = 2.38$; $P = 0.0115$ and $\chi2 = 6.56$; $P = 0.0105$) and the complete completion of the course of therapy by all patients.

Table 3

Results of a prospective randomized comparative clinical study of the frequency of *H. pylori* eradication and adverse effects depending on the prescribed treatment (stage I).

Treatment Protocols	n	Eradication % (95 % CI)	Adverse Effects % (95 % CI)
Omeprazole 0.04 g / day Clarithromycin 1 g / day Amoxicillin 2 g / day 98	98 93	ITT 78,6 (70,4—86,8) PP 82,8 (75,1—90,5)	ITT 24,5 (15,9—33,1) PP 25,8 (16,8—34,8) stopped treatment ITT 5,1 (0,7—9,5) PP 5,4 (0,8 %-10,0)
Omeprazole 0.04 g / day Clarithromycin 1 g / day Amoxicillin 2 g / day Lycopid 0.001 g / day 38	38 37	ITT 94,7 % (87,5—100) PP 97,3 % (91,7—100)	ITT 2,6 (0,01—7,7) PP 2,7 (0,01—7,8) stopped treatment- 0

Таблица 3

Результаты проспективного рандомизированного сравнительного клинического исследования частоты эрадикации *H.pylori* и побочных реакций в зависимости от назначенного лечения (I этап)

Протоколы лечения	n	Эрадикация % (95 % ДИ)	Побочные реакции % (95 % ДИ)
Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут	98 93	ITT 78,6 (70,4—86,8) PP 82,8 (75,1—90,5)	ITT 24,5 (15,9—33,1) PP 25,8 (16,8—34,8) прекратили лечение ITT 5,1 (0,7—9,5) PP 5,4 (0,8 %-10,0)
Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут Ликопид 0,001 г/сут	38 37	ITT 94,7 % (87,5—100) PP 97,3 % (91,7—100)	ITT 2,6 (0,01—7,7) PP 2,7 (0,01—7,8) прекратили лечение — 0

After 1 months (end of stage 1 of the study) after eradication therapy, according to the morphological method and rapid urease test, *H.pylori* was absent in the stomach and in the sections of the mucous membrane of the mucous membrane of the duodenal bulb in all patients included in the next phase of the clinical study (table 4).

Relapse of *H.pylori* infection 6 months after per protocol treatment: OCA - 3.9 % (95 % CI: 0.01-8.3 %; n = 3), OCAL - 0 %. Relapse of *H.pylori* infection 1 year after per protocol treatment: OCA - 5.2 % (95 % CI: 0.2-10.2 %; n = 4), OCAL - 0 % (Table 4). As follows from the results of the study, GMDP eliminates *H.pylori* during 12 and 24 months and was decreased after 5 and 10 years.

Table 4

Diagnosis of *H. pylori* after 1 months, 6 months, 1 year, 2 years, 5 years and 10 years after treatment

Groups	*Helicobacter pylori*									
	n	1 months	6 months	1 year	n	2 years	n	5 years	n	10 years
OCA	77	-	3	4	72	9	68	13	67	23
OCAL	36	-	-	-	36	-	36	1	35	2

Таблица 4

Диагностика *H.pylori* через 1 месяца, 6 месяцев, 1 год, 2 года, 5 лет и 10 лет после лечения

Группы	*Helicobacter pylori*									
	n	1 месяц	6 месяцев	1 год	n	2 года	n	5 лет	n	10 лет
ОКА	77	-	3	4	72	9	68	13	67	23
ОКАЛ	36	-	-	-	36	-	36	1	35	2

The frequency of *H.pylori* reinfection 2 years after per protocol treatment: OCA - 12.5 % (95 % CI: 4.8-20.2 %; n = 9), OCAL - 0 %. The frequency of *H.pylori* reinfection 5 years after per protocol treatment: OCA – 19.1 % (95 % CI: 9.7-28.5 %; n = 13), OCAL – 2.8 % (95 % CI: 0 , 01-8.3 %; n = 1). The frequency of *H. pylori* reinfection 10 years after per protocol treatment: OCA – 34.3 % (95 % CI: 22.8-45.8 %; n = 23), OCAL - 5.7 % (95 % CI: 0, 01-13.5 %; n = 2; Table 3). Thus, in patients taking Licopid at a dose of 1 mg per day together with anti-*Helicobacter pylori* therapy (the OCAL group), there was no *H.pylori* reinfection 2 years after per protocol treatment compared to the 10-day three-component treatment protocol without Lycopid. At the second stage of the study, it was also found that patients who took Licopid at the above dose together with three-component anti-bacterial therapy (OCAL group) had a significantly low frequency of *H. pylori* reinfection for 5 years ($\chi 2 = 4.33$; $P = 0.0375$) and 10 years ($\chi 2 = 6.73$; $P = 0.0095$).

The choice of patients with localization of an ulcer in the duodenal bulb (duodenal ulcer) as participants in a clinical study was based on the fact that, with duodenal ulcer of onion localization, a maximum degree of contamination of *H.pylori* gastric mucosa was observed (99.0 %) [38] and sections of gastric metaplasia of the mucous membrane of the duodenal bulb (87.8 %) [39].

The choice of Licopid as an immunomodulator therapy in the 10-day *H.pylori* eradication scheme was consistent with the concept of an "ideal" immunomodulator and was based on three main criteria, according to current scientific research data [40]:

The first criterion includes the presence of N-acetyl-glucosaminyl-N-acetylmuramyl dipeptide. One of the reasons for the ineffectiveness of eradication therapy is the transition of *H.pylori* to metabolically inactive forms (coccoid and U-form) that are resistant to antibiotics. It was previously shown that glucosaminyl muramil dipeptide promoted the release of *Mycobacterium tuberculosis* from the dormant form, which, apparently, determines the effectiveness of Licopid therapy [41]. Similarly, it was previously shown that NOD1 and NOD2 receptor activation promotes the elimination of *H.pylori* [42, 43]. The active substence of Lycopide, N-acetylglucosaminyl-N-acetylmuramyl dipeptide (GMDP, glucosaminyl muramyl dipeptide), is the main complete repeating structural unchanged fragment of the cell wall of almost all known bacteria, a ligand of NOD2 receptors.

According to the second criterion for "ideal" immunomodulator it is necessary to activate immune system through T helper 1 lymphocytes. It was shown that activation immune answer through T helper 1 lymphocytes is essential for successful treatment *H. pylori* [44-47]. GMDP fully complies with the second criterion - its influence on the balance T helper 1/ T helper 2 shift towards T helper 1 has been proven [21, 22, 48].

By the third criterion an "ideal" immunomodulator has a bacterial, probiotic origin. According to Regulation 9 of Working Group 5 (Consensus Maastricht V) [2] and based on 14 meta-analyzes of RCTs (2007–2019) [49–62], which combined 259 RCTs with 41727 patients, the addition of *Lactobacillus* strains optimizes therapy and decreases adverse effects.

These meta-analyzes found that specific strains of *Lactobacillus* or several probiotic strains increase eradication of *H.pylori* by 8.1 % and reduce the number of adverse reactions when using the probiotic 14 days before eradication therapy or during eradication therapy. Bifidobacterium and Saccharomyces boulardii did not affect the level of eradication during anti- Helicobacter therapy [58, 62]. The use of specific strains of probiotics (*Lactobacillus bulgaricus, Lactobacillus acidophilus, Lactobacillus casei DN-114001, Lactobacillus gasseri, and Bifidobacterium infantis 2036*) during eradication therapy can be considered as an option to increase the level of *H.pylori* eradication, especially when the antibiotic is not effective [63, 68]. The effect of probiotics on the reduction of adverse reactions during eradication therapy has been proven [62]. A significant increase in the eradication of *H.pylori* by 17 % was found using mainly specific strains of Lactobacillus. When multicomponent probiotics were used as adjuvant therapy, eradication increased by only 2.8 % [54]. Monotherapy with probiotics using specific strains of Lactobacillus led to significant ($P < 0.001$), compared with placebo, eradication of *H.pylori* in 16 % of patients, using multicomponent probiotics (which included Lactobacillus strains) in 14 % of patients [63].

Interestingly, that GMDP was for identified the first time as a fragment of Lactobacillus bulgaricus cell wall [64] and thus its beneficial effect in *H.pylori* therapy is consistent with the data of the above studies.

Based on the data obtained, it can be concluded that therapy with the immunomodulator Licopid in a 10-day *H.pylori* eradication scheme demonstrated an encouraging result. GMDP maintaines the long term (2, 5 and 10 years) eradication of *H.pylori* in 100 %, 98 % and in 95 % of cases. The reinfection of *H.pylori* after 5 years of the treatment is observed in 32 %–91,4 % cases [8, 9, 65]. Thus, the method for optimizing *H. pylori* therapy proposed in this research is in demand and has practical significance.

Conclusions

GMDP at a dose of 0.001 g per day during 10-day three-component anti-Helicobacter therapy significantly increased *H.pylori* eradication by 16 % (according to ITT; $\chi 2 = 3, 87$; $P = 0.0492$) and by 14.5 % (according to PP; $\chi 2 = 4.0$; $P = 0.0455$), with a significant decrease in the frequency of adverse reactions from the gastrointestinal tract by 2.5 % (according to ITT; $\chi 2 = 2.38$; $P = 0.0115$) and 2.7 % (according to PP; $\chi 2 = 6.56$; $P = 0.0105$) and the completion of the course of therapy by all patients. GMDP maintain the absence of *H.pylori* in 100 % during 2 years, in 98 % after 5 years and in 95 % after 10 years after treatment.

Triple antibiotic eradication therapy of *H. pylori*, eliminates both pathogenic and commensal microorganisms, the waste products of which are vital and maintain immune homeostasis, including via NOD2 receptors of innate immunity. The success of the complex *H.pylori* eradication treatment can be explained by the compensatory effect of the GMDP for the missing signal from commensals for innate immunity receptors, providing an adequate immune response and preventing chronicity and recurrence of the infection.

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