



Prof. L.S. Babinets¹, prof. O.O. Abrahamovych²

¹ I. Horbachevsky Ternopil National Medical University

² Danylo Halytsky Lviv National Medical University

Hepatotropic therapy efficiency in the management of a comorbid patient with chronic pancreatitis after etiotropically treated chronic viral hepatitis C

The management of comorbid pathologies is an important component of the activities of doctors in almost all specialties, but this is most relevant in general medical practice at the stage of primary health care. It is known that the combination of diseases in one patient makes the clinical course more severe, prospectively less optimistic, leads to the formation of complications. In addition, the problem of medicine around the world is the lack of protocols for the management of patients with comorbid conditions, which requires research by scientists and practitioners [4]. The comorbidity of chronic pancreatitis (CP) and chronic viral hepatitis C (CVHC) is quite common and problematic, even after etiological treatment of viral hepatitis C infection [2, 12]. Scientists believe that among the etiological factors in the formation of CP, the alcohol factor (from 25.0 to 80.0%), a large position is occupied by pathologies of the hepatobiliary system (from 25 to 40%), as well as the infectious factor [1, 8, 11]. According to Babinets L.S. et al., 2007, 2021, when analyzing significant etiological factors in the formation of the disease among 218 patients with CP, the following figures of the influence of these factors were established: alcohol — 8.26%, hepatobiliary — 44.50%, gastroduodenal — 51.37%, infectious — 56.88%, ischemic — 20.18%, allergic — 8.33%, post-traumatic — 16.67%, after acute pancreatitis — 7.80% [1, 3]. Most patients had a mixed genesis of CP, so the factors were often insisted [13]. This state of affairs drew attention to the significance of infectious and hepatobiliary factors.

Among the infectious agents, the most relevant causes of occurrence or complication of the clinical course of CP are viral hepatitis C, B and D, for which the ability to chronify the infection has been proven. These viruses have identical routes of spread (including through blood and blood products) and prolonged persistence in the body [6, 10]. One of the most important discoveries

in recent years has been the establishment of the fact of replication of HBV and HCV viruses in tissues of lymphatic and non-lymphatic origin, which led to the elucidation of the pathogenesis of multisystem damage observed in these infections [14, 15]. This approach allows us to consider viral hepatitis not only as a liver disease, but also as a systemic (generalized) infection that affects other organs, in particular, the pancreas (PG) [9]. According to expert estimates, about 3.6% (about 1.5 million people) live with CVHC in Ukraine, but only 5.4% are under medical supervision [2]. Ukraine belongs to countries with an average prevalence of viral hepatitis C. However, according to the results of selective monitoring of risk groups, the level of infection with hepatitis C virus among some of them significantly exceeds the global average and reaches 40–60%. And although viral hepatitis C is curable in 95%, a significant number of patients do not know about their diagnosis and do not have access to treatment. Treatment has become affordable in price (the cost of the course has decreased from \$900 to \$100), so identifying patients with viral hepatitis C is an urgent problem, especially at the primary care level [10].

At the same time, it should be noted that significant progress has been made today in the treatment of patients with hepatitis C, it can now be considered a curable disease [7]. In addition, research in this area continues, and new drugs can significantly improve treatment efficacy. Timely detection of the disease, determination of its stage and prescription of optimal treatment regimen are very important in achieving the main goal of treatment — persistent virologic response. Studying the consequences of CVHC, even etiotropically treated, including for the state of the pancreas (PG) in CP, is also an important issue.

Aim — to investigate the state of the functional ability of the pancreas and general clinical and selected

biochemical parameters of patients with CP against the background of treated CVHC under the influence of the proposed complex treatment with additional inclusion of the hepatotrophic drug Heparizin.

Materials and methods. Data from form 025/o «Outpatient Medical Records» and form 003/o «Inpatient Medical Records» of 45 patients with CP comorbid with CVHC were analyzed. All patients were examined according to generally accepted algorithms and received a generally accepted complex treatment protocol (GAT) for CP in accordance with the order of the Ministry of Health of Ukraine No. 638 dated 2014 and CVHC — according to the Clinical Guidelines of the Ministry of Health of Ukraine based on evidence «Viral hepatitis C» from 2020 [4, 5]. The control group consisted of 25 practically healthy people comparable in age and sex.

The criterion for inclusion in the study group of patients with CP in combination with CVHC were patients with CP who were diagnosed with viral hepatitis C in connection with an exacerbation or as an accidental finding. All etiologically treated by the standard method in accordance with the recommendations of the Clinical Guidelines based on evidence «Viral Hepatitis C» created by the working group by order of the Ministry of Health of Ukraine dated 18.08.2020 No. 1908, based on the recommendations of WHO «Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection» (2018) and «EASL Recommendations on Treatment of Hepatitis C» (2020). Regardless of the established HCV genotype, patients received a course of treatment with Sofosbuvir at a dose of 400 mg and Velpatasvir 100 mg in the morning after a meal for 3 months (some patients received Daclatasvir instead of Velpatasvir at a dose of 60 mg also in the morning after eating for 3 months). The period after the stated and treated viral hepatitis C before the examination was on average (2.35 ± 0.61) years [4, 10].

Exclusion criteria: diabetes mellitus, hepatitis and cirrhosis in the exacerbation phase, including viral etiology, cholelithiasis with existing calculi, acute and chronic diseases of vital organs and systems, oncological diseases, patient refusal to participate in the study.

Among the analyzed patients there were 55% women and 45% men. The age of the patients ranged from 29 to 69 years. The average age was (49.57 ± 10.89) years.

Biochemical studies to assess the clinical course of CP and CVHC, as well as the nutritional status of patients were performed on a Vitalab Flexor-2000 analyzer (Netherlands).

Exocrine pancreatic insufficiency (EPI) was traditionally determined by the content of fecal elastase-1 (FE-1), which was determined by ELISA using standard kits from BIOSERV ELASTASE 1-ELISA.

All patients with a comorbid course of CP and CVHC who underwent an outpatient course of rehabilitative treatment in a primary care setting at the place of residence were divided into 2 groups according to the principles of randomization to study the effectiveness of the proposed correction programs:

Group 1 (20 patients with CP and CVHC) received a generally accepted treatment protocol (GAT) for three

months, which included normalization of lifestyle and dietary recommendations, a pure pancreatin enzyme preparation in an adequate dose (25–40 lipase units) during meals constantly, a proton pump inhibitor (pantoprazole 40 mg), an antispasmodic (mebeverine) and/or a prokinetic (motilium) — as needed. Mandatory components of the GAT were outpatient care, diet according to the order of the Ministry of Health of Ukraine dated 29.10.2013 No. 931, taking into account the recommendations of tables 5 and 5p according to Pevzner.

Group 2 (GAT+HZ) — 25 patients with CP and CVHC) — received GAT with the additional inclusion of the hepatotrophic agent Heparizin PLC 1 capsule 3 times a day after meals for 3 months.

The motivation for including Heparizin PLC (Valartin Pharma, LLC; Ukraine) in the GAT is the need to strengthen the liver as an organ of metabolic detoxification, protein synthesis, improvement of biliary synthesis and passage, etc. One HZ capsule contains glycyrrhizin — 50 mg; glycine — 50 mg; DL-methionine — 50 mg; phospholipids (PL) — 217 mg (equivalent to 65 mg of phosphatidylcholine). It is known that PLs contained in the composition of HZ are chemically analogous to endogenous PLs, but greatly surpass them due to the high content of polyunsaturated (essential) fatty acids. These high-energy molecules are predominantly incorporated into the structures of cell membranes and promote the restoration of damaged liver tissues. PLs affect disturbed lipid metabolism by regulating lipoprotein metabolism, resulting in neutral fats and cholesterol being converted into transport active forms. When PLs are excreted through the biliary tract, the lithogenic index decreases, and bile stabilizes. PLs also improve the lipophilic properties of glycyrrhizinic acid, increasing the intensity and speed of its absorption more than 2 times. HZ was recommended as an additional source of the essential sulfur-containing amino acid methionine and natural biologically active components. Glycine is a replaceable amino acid that stimulates the formation of glycogen by the liver, regulates metabolism, has antitoxic, antioxidant, detoxifying and hepatoprotective properties. Glycyrrhizin (potassium and calcium salts of glycyrrhizinic acid), the structural similarity of which with hormones determines its biological activity (anti-inflammatory, antifibrotic, antiallergic, antiviral, immunomodulating properties) and phosphatidylcholine (the main component of PL), which is the main structural element membranes and able to restore their structure and function when damaged, exhibiting a protective effect.

This HZ is recommended to improve the functional state of the liver and prevent complications in chronic hepatitis, including viral origin, and other diffuse liver diseases, for effective antiviral protection against the penetration of viruses, to increase mental performance and even improve skin condition and create optimal conditions for body functioning in psoriasis, dermatitis and eczema. There were no contraindications (hypersensitivity to components, acute viral hepatitis, arterial hypertension, pregnancy and lactation period) for prescribing HZ to our patients.

In addition, we did not find any information in the scientific and educational medical literature regarding the feasibility and effectiveness of using this drug in CP. This motivated the study.

Results and discussion. An important stage of the study was to conduct a comparative analysis of the dynamics of parameters of the functional and structural state of the pancreas in patients with comorbidity of CP and CVHC under the influence of GAT and GAT+HZ (Table 1).

According to Table 1, a more significant level of effectiveness of the treatment complex with the additional

inclusion of Heparizin was established in relation to such a GAT: the content of fecal α -elastase increased by 54.4% versus 39.9%, glucose content decreased by 15.6% versus 10.0%, the coprogram score decreased by 40.2% versus 25.1%, the ultrasound score of the pancreatic structure decreased by 74.4% versus 33.6% ($p<0.05$). Thus, the inclusion of Heparizin in the standard therapy of CP with CVHC improved treatment outcomes with the restoration of the functional and structural state of the pancreas according to the studied parameters.

Table 1 — Comparative analysis of the dynamics of parameters of the functional and structural state of the pancreas in patients with CP and CVHC under the influence of treatment programs

Indicator of pancreatic functional state	Comparison group				
	Control group (n=25)	Group 1 (GAT) (n=20)		Group 2 (GAT+HZ) (n=25)	
		Before treatment	After treatment	Before treatment	After treatment
α -elastase, $\mu\text{g/g}$	242,58±6,24	110,85±3,17*	155,11±6,16**	110,49±3,45*	170,57±6,20***
Blood glucose, mmol/l	4,78±0,08	5,43±0,46*	4,42±0,26**	5,65±0,43*	4,97±0,28***
Coprogram score	0,09±0,02	5,58±0,28*	4,46±0,19**	5,48±0,61*	3,91±0,28***
Ultrasound score of pancreatic structure	1,05±0,03	6,24±0,63*	4,67±0,56**	6,26±0,59*	3,59±0,81**
Notes: 1* — probable difference in indicators relative to the control group ($p<0.05$); 2** — probable difference in indicators in their group after treatment relative to those in their group before treatment ($p<0.05$); 3 — probable difference in indicators after treatment in the GAT+HZ group relative to those in the GAT group after treatment ($p<0.05$).					

Conclusions: A more significant level of effectiveness of the treatment complex with the additional inclusion of the hepatotrophic drug Heparizin was established in relation to such protocol treatment regarding the restoration of the functional and structural state of the pancreas according to the studied parameters: the content of fecal α -elastase increased by 54.4% versus 39.9%, glucose content decreased by 15.6% versus 10.0%, the coprogram score decreased by 40.2% versus 25.1%, the ultrasound score of the pancreatic structure decreased by 74.4% versus 33.6% ($p<0.05$); the reliable positive effect of Heparizin on the disturbed parameters

of the functional state of the pancreas in CP in combination with CVHC has been proven and it allowed to assert its optimizing effect on pancreatic function; it is recommended to additionally include the hepatotrophic agent Heparizin in the protocol complex therapy of patients with CP against the background of etiologically treated CVHC at the stage of outpatient rehabilitative treatment.

In the perspective of further research, we plan to investigate the effectiveness of the proposed treatment on the immune status of patients with CP comorbid with treated CVHC.

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Ефективність гепатотрофної терапії у веденні коморбідного пацієнта із хронічним панкреатитом після етіотропно пролікованого хронічного вірусного гепатиту С

Проф. Л.С. Бабінець¹, проф. О.О. Абрагамович²

¹ Тернопільський національний медичний університет імені І.Я. Горбачевського МОЗ України

² Львівський національний медичний університет імені Данила Галицького

Актуальність. Коморбідність хронічного панкреатиту (ХП) і хронічного вірусного гепатиту С (ХВГС) є доволі частою і проблемною, навіть після проведення етіотропного лікування інфекції вірусного гепатиту С.

Мета – дослідити стан функціональної здатності підшлункової залози та загальноклінічних і вибраних біохімічних параметрів пацієнтів із ХП на тлі пролікованого ХВГС під впливом запропонованого комплексного лікування із додатковим включенням гепатотрофного препарату гепаризину.

Матеріали та методи. Було досліджено 45 хворих на ХП у коморбідності із ХВГС. Всі хворі були обстежені за загальноприйнятими алгоритмами і отримували загальноприйнятий комплекс лікування за протоколом (ЗПК) ХП згідно із наказом МОЗ України № 638 від 2014 р. та ХВГС – за Клінічною настановою МОЗ України, заснованою на доказах «Вірусний гепатит С» від 2020 р. Усіх амбулаторних пацієнтів з коморбідним перебігом ХП і ХВГС розділили на 2 групи для вивчення дієвості запропонованих програм корекції: 1 група (20 пацієнтів) отримувала загальноприйнятий комплекс лікування за протоколом (ЗПК) протягом трьох місяців, 2 група (ЗПК+ГЗ) – 25 пацієнтів із ХП і ХВГС) – отримували ЗПК із додатковим включенням гепатотрофного засобу Гепаризин РЛС по 1 капсулі 3 рази на добу після прийому їжі протягом 3 місяців.

Результати та обговорення. Встановили більш значимий рівень ефективності лікувального комплексу із додатковим включенням гепатотрофного препарату гепаризину стосовно такого протокольного лікування щодо відновлення функціонального і структурного стану ПЗ за даними досліджених параметрів: вміст фекальної α -еластази підвищувався відповідно на 54,4 % проти 39,9 %, вміст глюкози знижувався – на 15,6 % проти 10,0 %, бальний показник копрограми знижувався – на 40,2 % проти 25,1 %, бальний УЗ-показник структури ПЗ знижувався – на 74,4 % проти 33,6 % ($p < 0,05$).

Висновки: Доведено достовірний позитивний вплив гепаризину на порушені параметри функціонального стану ПЗ при ХП у поєднанні із ХВГС і дозволило стверджувати про протизапальну активність гепаризину, оптимізуючий його вплив на ПЗ. Рекомендовано додаткове включення гепатотрофного засобу гепаризину до протокольної комплексної терапії хворих на ХП на тлі пролікованого етіологічно ХВГС на етапі відновного амбулаторного лікування.

Ключові слова: хронічний панкреатит, хронічний вірусний гепатит С, гепатотрофний засіб гепаризин, комплексне відновне лікування, фекальна еластаза-1.

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Prof. L.S. Babinets¹, prof. O.O. Abrahamovych²

¹ I. Horbachevsky Ternopil National Medical University

² Danylo Halytsky Lviv National Medical University

Summary. Relevance. Comorbidity of chronic pancreatitis (CP) and chronic viral hepatitis C (CVHC) is quite common and problematic, even after etiologic treatment of viral hepatitis C infection.

The aim is to investigate the state of the functional capacity of the pancreas and general clinical and selected biochemical parameters of patients with CP against the background of treated CVHC under the influence of the proposed complex treatment with the additional inclusion of the hepatotropic drug heparizin (HZ).

Materials and methods. 45 patients with CP comorbid with CVHC were studied. All patients were examined according to generally accepted algorithms and received a generally accepted complex of treatment according to the protocol (GAT) for CP in accordance with the order of the Ministry of Health of Ukraine No. 638 dated 2014 and CVHC — according to the Clinical Guideline of the Ministry of Health of Ukraine, based on evidence «Viral Hepatitis C» dated 2020. All outpatient patients with a comorbid course of CP and CVHC were divided into 2 groups to study the effectiveness of the proposed correction programs: 1 group (20 patients) received a generally accepted complex of treatment according to the protocol (GAT) for three months, Group 2 (GAT+HZ) — 25 patients with CP and CVHC) — received GAT with the additional inclusion of the hepatotropic agent Heparizin PLC, 1 capsule 3 times a day after meals for 3 months.

Results and discussion. A more significant level of effectiveness of the treatment complex with the additional inclusion of the hepatotropic drug heparizin was established in relation to this protocol treatment for the restoration of the functional and structural state of the pancreas according to the studied parameters: the content of fecal α -elastase increased by 54.4% vs. 39.9%, respectively, and glucose content decreased — by 15.6% vs. 10.0%, the co-program score decreased — by 40.2% vs. 25.1%, the US score of the software structure decreased — by 74.4% vs. 33.6% ($p < 0.05$).

Conclusions: The reliable positive effect of heparizin on the disturbed parameters of the functional state of the pancreas and liver in CP in combination with CVHC was proven and allowed to assert the anti-inflammatory activity of heparizin, optimizing its effect on protein metabolism and functions of the pancreas and liver. It is recommended to additionally include the hepatotropic agent heparizin to the protocol complex therapy of patients with chronic pancreatitis against the background of treated etiologically CVHC at the stage of outpatient rehabilitative treatment.

Key words: chronic pancreatitis, chronic viral hepatitis C, hepatotropic agent Heparizin, complex rehabilitative treatment, fecal elastase-1.

Контактна інформація: Бабінець Лілія Степанівна —
д-р мед. наук, професор, завідувач кафедри терапії та сімейної медицини
Тернопільського національного медичного університету імені І.Я. Горбачевського МОЗ України,
lilyababinets@gmail.com, 0673520743. ORCID: <https://orcid.org/0000-0002-0560-1943>;
SCOPUS: 56561149600

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