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DYNAMICS OF MARKERS OF INTRAHEPATIC CHOLESTASIS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS WHEN APPLYING AN INTEGRATED PROTEIN-AMINO ACID AND VITAMIN PRODUCT (MARE'S MILK)

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Abstract

Introduction: Primary biliary cholangitis (PBC), formerly primary biliary cirrhosis, is a rare progressive cholestatic liver disease, whose hallmark features include a persistently elevated alkaline phosphatase level, presence of anti-mitochondrial antibodies (AMA) and characteristic histology. For 30 yearsursodeoxycholic acid (UDCA), a bile acid, has been the only available therapeutic agent. PBC is associated with the development of end-stage liver disease, increased morbidity and mortality. UDCA has been shown to improve serum biochemistries, histology and delay the need for liver transplantation. The clinical issue is that approximately 25%-40% of patients do not respond to this standard therapy. In recent years, many trials have investigated alternative and adjunctive treatments**.**In way of the search for a safe and effective treatment for PBC mares milk acquires high potential in terms of affecting one of the links in the pathogenesis of PBC by modeling the composition of the intestinal microbiome. The intestinal microbiome plays an important role in the pathogenesis of PBC by regulating bile acid metabolism and immune responses.

The aim of the study – to evaluate the effect of a complex protein-amino acid and vitamin product (mares milk) on the indicators of markers of intrahepatic cholestasis in patients with PBC (primary endpoint).

Material and methods of the study. From September 2018 to the present time, an interventional non-randomised clinical trial (identifier NCT03665519) has been conducted in National Scientific Medical Center and currently, 23 patients have completed the study. Inclusion criteria: Patients with verified diagnosis of PBC, aged 18 to 75 years. Exclusion criteria: alcohol and/or drug dependence, presence of liver cirrhosis class C based on Child Pugh classification, allergic reaction to dairy products, pesence of mental diseases, severe concomitant pathology, regnancy and/or lactation, lactose intolerance. Participants from experimental (main) group were administered a supplement (sublimated mare milk 40 g/day) for 3 months accompanied with standard UDCA therapy (dosage of 15/kg/day). PBC patients from control group were administered only UDCA therapy (dosage of 15/kg/day). Markers of intrahepatic cholestasis were evaluated: gamma-glutamyltranspeptidase (GGT) and alkaline phosphatase (ALP) at the beginning of the study and after 3 months in patients of both groups.

Comparison of the dynamics between the groups was carried out in the context of visits using the one-way analysis of variance based on the Fisher criterion and the non-parametric Kruskal-Wallis test.

The level of statistical significance in the comparative analysis was adopted at 0.95 ($\alpha = 0.95$). It means the expected level of reliability, statistical significance, at which the null hypothesis of the absence of statistical differences in the comparative analysis is rejected, should be less than 0.05 ($p < 0.05$).

The results of the study. In patients of the main group, the level of ALP was significantly reduced to 6,72 ± 0,632 compared with the observation in the control group (9,30 ± 1,553). Comparing the dynamic level of GGTP in patients of the main group, this indicator was significantly reduced to 3.88 ± 0.611 compared with the control group (5.53 ± 0.770). The study showed a significant decrease in the main markers of intrahepatic cholestasis in patients with complex protein-protein and vitamin product (mare's milk).

The conclusion: The study showed a significant decrease in the main markers of intrahepatic cholestasis in patients after taking complex protein-amino acid and vitamin product (mares milk). Thus, the use of mares milk is an effective addition to the standard therapy of PBC.

Key words*: primary biliary cholangitis, cholestasis, microbiome, mares milk.*

Резюме

ДИНАМИКА МАРКЕРОВ ИНТРАГЕПАТИЧЕСКОГО ХОЛЕСТАЗА У ПАЦИЕНТОВ С ПЕРВИЧНЫМ БИЛИАРНЫМ ХОЛАНГИТОМ ПРИ ПРИМЕНЕНИИ КОМПЛЕКСНОГО ПРОТЕИН-АМИНО-КИСЛОТНОГО И ВИТАМИННОГО ПРОДУКТА (САУМАЛ)

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Актуальность. Первичный билиарный холангит (ПБХ), известный ранее как первичный билиарный цирроз - это редкое прогрессирующее холестатическое заболевание печени, отличительными признаками которого являются повышенный уровень щелочной фосфатазы, обнаружение антимитохондриальных антител (АМА) и характерная гистологическая картина. В течение почти 30 лет урсодезоксихолевая кислота (УДХК), является единственным доступным терапевтическим средством. ПБХ связан с развитием терминальной стадии заболевания печени (цирроза), повышенной заболеваемостью и смертностью. Было показано, что УДХК улучшает биохимические показатели, гистологическую картину и задерживает необходимость трансплантации печени. Клиническая проблема заключается в том, что приблизительно 25-40% пациентов не реагируют на стандартную терапию УДХК. В последние годы во многих исследованиях были исследованы альтернативные и дополнительные методы лечения. В свете поиска безопасного и эффективного метода лечения кобылье молоко приобретает высокий потенциал в плане воздействия на одно из звеньев патогенеза ПБХ путем моделирования композиции кишечного микробиома. Микробиом кишечника играет важную роль в этиопатогенезе ПБХ путем регулирования метаболизма желчных кислот и иммунных реакций.

Цель данного исследования: оценить влияние комплексного белково-аминокислотного и витаминного продукта (кобыльего молока) на показатели маркеров внутрипеченочного холестаза у больных с ПБХ.

Материалы и методы исследования: с сентября 2018 года по настоящее время на базе Национального научного медицинского центра проводится экспериментальное нерандомизированное клиническое исследование (clinicaltrials.gov identifier NCT03665519), Критериями включения были возраст от 18 лет, наличие верифицированного диагноза ПБХ, согласие на участие в исследовании. Критерии исключения: алкогольная и наркотическая зависимость, наличие цирроза печени класс С по Чайлд-Пью, наличие известной аллергии на молочные продукты, психические заболевания, тяжелая сопутствующая патология, беременность и/или лактация, непереносимость лактозы. В настоящее время завершили исследование 23 пациента (14 – из основной группы, 9 – из контрольной группы). Основную группу составили 14 человек, пациенты этой группы в дополнение к стандартной терапии (препараты урсодезоксихолевой кислоты) в течение 3 месяцев употребляли белково-аминокислотный и витаминный продукт (сублимированное кобылье молоко, разведенное в воде) в дозе 40 г в сутки. В контрольную группу вошли 9 человек, участники этой группы получали только стандартную терапию ПБХ. Оценивались маркеры внутрипеченочного холестаза: гамма-глютамилтранспептидаза (ГГТП) и щелочная фосфатаза (ЩФ) в начале исследования и через 3 месяца у пациентов обеих групп.

Сравнение динамики между группами проводилось в контексте визитов с использованием одностороннего дисперсионного анализа на основе критерия Фишера и непараметрического критерия Крускала-Уоллиса.

Уровень статистической значимости в сравнительном анализе был принят на уровне 0,95 ($\alpha = 0,95$). Это означает, что ожидаемый уровень достоверности, статистической значимости, при котором отвергается нулевая гипотеза об отсутствии статистических различий в сравнительном анализе, должен быть менее 0,05 ($p < 0,05$).

Результаты исследования: у пациентов основной группы уровень ЩФ был достоверно снижен до 6,72 ± 0,632 по сравнению с наблюдением в контрольной группе (9,30 ± 1,553). Сравнивая динамику уровня ГГТП, у пациентов основной группы данный показатель был достоверно снижен до 3,88 ± 0,611 по сравнению с группой контроля (5,53 ± 0,770). Исследование показало достоверное снижение основных маркеров внутрипеченочного холестаза у пациентов на фоне приема комплексного белково-аминокислотного и витаминного продукта (кобылье молоко).

Выводы: таким образом, применение сублимированного кобыльего молока может стать эффективным многообещающим дополнением к стандартной терапии ПБХ.

Ключевые слова: *первичный желчный холангит, холестаз, микробиом, кобылье молоко.*

Түйіндеме

БІРІНШІЛІК БИЛИАРЛЫ ХОЛАНГИТКЕ ШАЛДЫҚҚАН НАУҚАСТАРДЫҢ ПРОТЕИН-АМИН ҚЫШҚЫЛДЫ ВИТАМИН ӨНІМІ (САУМАЛ) ҚОЛДАНУДАҒЫ ИНТРАГЕПАТИКАЛЫҚ ХОЛЕСТАЗ МАРКЕРЛЕРІНІҢ ДИНАМИКАСЫ

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Өзектілігі. Бұрын бастапқы билиарлы цирроз ретінде белгілі біріншілік билиарлы холангит ағзада сілтілік фосфатаза деңгейінің жоғарылауы, антимитохондриялық антиденелерді (АМА) анықталуы, сондай – ақ сәйкес гистологиялық көрініспен ерекшеленетін бауырдың сирек прогрессивті холестатикалық ауруы болып табылады. 30 жылға жуық уақыт бойы урсодеоксикол қышқылы жалғыз қол жетімді емдік агент болып келді. Біріншілік биллиарлы холангит бауыр ауруының (цирроз), сатылы аурудың және өлімнің жоғарылауымен байланысты. Урсодеоксил қышқылы биохимиялық параметрлерді, гистологиялық көріністі жақсартып, бауыр трансплантациясының қажеттілігін кешіктіретіні көрсетілді. Клиникалық мәселе - науқастардың шамамен 25–40% - ына урсодексил қышқылымен жүргізілетін стандартты терапия әсері болмайды. Соңғы жылдары көптеген зерттеулер балама және қосымша терапияны зерттеді. Емдеудің қауіпсіз және тиімді әдісін іздестіру кезінде саумалмен емдеу ішек микробиомының құрамын модельдеу арқылы біріншілік биллиарлы холангит патогенезіндегі байланыстардың біріне әсер ету тұрғысынан үлкен әлеуетке ие болады. Ішек микробиомы өт қышқылдарының метаболизмі мен иммундық реакцияларды реттей отырып, біріншілік биллиарлы холангит этиопатогенезінде маңызды рөл атқарады.

Зерттеудің мақсаты: күрделі ақуыз-амин қышқылы мен витаминдік өнімнің (саумал) біріншілік биллиарлы холангитпен ауыратын науқастардағы бауырішілік холестаздың көрсеткіштеріне әсерін бағалау.

Зерттеу материалдары мен әдістері: Клиникалық сынақ (clinicaltrials.gov identifier NCT03665519) 2018 жылдың қыркүйегінен қазіргі уақытқа дейін Ұлттық ғылыми медициналық орталық негізінде жүргізілді, зерттеуге 18 жасқа толған зерттеу шарттарымен толық танысып, рұқсаттама алынған науқастар іріктеліп алынды. Шығару критерийлері: алкогольге және есірткіге тәуелділік, Child-Pugh сәйкес С тобындағы бауыр циррозының болуы, сүт өнімдеріне белгілі аллергия, психикалық ауру, ауыр патология, жүктілік және / немесе лактация, лактозаға төзбеушілік. Қазіргі уақытта 23 науқас зерттеуді аяқтады (негізгі топтан 14, бақылау тобынан 9). Негізгі топ 14 адамнан тұрды, осы топтың пациенттері стандартты терапиядан басқа (урсодеоксил қышқылына арналған препараттар) 3 ай бойы күніне 40 г дозада ақуыз-амин қышқылы мен витаминді өнімді (сублимацияланған саумал,) тұтынды. Бақылау тобы 9 адамнан тұрды, осы топтың қатысушылары тек біріншілік билиарлы холангит үшін стандартты терапияны алды. Жүрекішілік холестаздың белгілері бағаланды: гамма-глутамилтранспептидаза (GGTP) және сілтілі фосфатаза (ALP) зерттеу басында және 3 айдан кейін екі топтың науқастары.

Топтар арасындағы динамиканы салыстыру Фишер сынағы және параметрлі емес Крускал-Уоллис сынағы негізінде дисперсияны бір жақты талдауды қолдана отырып бірнеше келулер уақытында жүргізілді.

Салыстырмалы талдауда статистикалық маңыздылық деңгейі 0,95 (α = 0.95) деңгейінде қабылданды. Бұл салыстырмалы анализде статистикалық айырмашылықтар жоқ деген болжам болған сенімділіктің, статистикалық маңыздылық деңгейі 0,05-тен ($p < 0.05$) кем болуы керек дегенді білдіреді.

Зерттеу нәтижелері: негізгі топтағы науқастар (6,72 ± 0,632) сілтілі фосфатаза деңгейін бақылау тобындағы нәтижелермен салыстырғанда (9.30 ± 1.553) едәуір төмендеді. ГГТП деңгейінің динамикасын салыстыра отырып, негізгі топтағы емделушілерде бұл көрсеткіш бақылау тобымен (5.53 ± 0.770) салыстырғанда 3,88 ± 0,611 дейіне азайды. Зерттеу күрделі ақуыз-амин қышқылды витаминдік өнім (саумал) бар емделушілерде ішілік холестаздың негізгі көрсеткіштерінің айтарлықтай төмендегенін көрсетті.

Қорытынды: Сонымен, сублимирленген саумалды қолдану біріншілік биллиарлы холангиттің стандартты терапиясына тиімді және перспективалы қосымша емдеу әдісі бола алады.

Негізгі сөздер: *біріншілік билиарлы холангит, холестаз, микробиом, саумал.*

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Background

Primary biliary cholangitis (PBC), formerly primary biliary cirrhosis, is a rare progressive cholestatic liver disease, whose hallmark features include a persistently elevated alkaline phosphatase level, presence of anti-mitochondrial antibodies (AMA) and characteristic histology. The prevalence of PBC in different countries varies and ranges from 40 to 400 cases of the disease per 1 million people; the highest values are recorded in northern Europe. Over the past decade, in some western regions, the prevalence of PBC has increased to 1 case per 700 people, a similar trend is observed in Kazakhstan.In the structure of mortality from cirrhosis of the liver of all types, the proportion of PBC is approximately 2% [1, 6, 7].

The results of studies carried out in the last 30 years made it possible to distinguish two main aspects of the etiology and pathogenesis of PBC - a genetic predisposition and trigger environmental factors [2,8].

Due to the lack of etiotropic therapy for PBC, the only justified pathogenetic treatment from the point of view of evidence-based medicine is the long-term, almost lifetime use of ursodeoxycholic acid. Treatment of patients with PBC with immunosuppressive drugs is ineffective or insufficiently effective.Taking the fact into consideration, that PBC is a slowly progressing disease, this ultimately leads to the need for liver transplantation [1, 3, 4].

However, liver transplantation is available only to a small percentage of patients due to the widespread deficiency of donor organs and the high cost of the procedure itself, the risk of complications associated with major surgery.

Despite improved survival with standard therapy, about 30% of patients with PBC show a lack of response to therapy and a poor prognosis. Orientation to the relationship between the exchange of bile acids and intestinal microbiome offers new perspectives for the treatment of PBC [5].

In way of the search for a safe and effective treatment for PBC mares milk acquires high potential in terms of affecting one of the links in the pathogenesis of PBC by modeling the composition of the intestinal microbiome. The intestinal microbiome plays an important role in the pathogenesis of PBC by regulating bile acid metabolism and immune responses.

The aim. To evaluate the effect of a complex protein-amino acid and vitamin product (mares milk) on the indicators of markers of intrahepatic cholestasis in patients with PBC.

Material and methods of the study.

From September 2018 to the present time, an interventional non-randomised clinical trial (clinicaltrials.gov identifier NCT03665519) has been conducted at the National Scientific Medical Center and currently, 23 patients with PBC have completed the study. All patients were recruited from the outpatient clinic of National Scientific Medical Center.

Inclusion criteria: Patients with verified diagnosis of PBC, aged 18 to 75 years. The diagnosis of PBC was based on the following three criteria:

1. biochemical evidence of cholestasis (elevation of alkaline phosphatase (ALP) in serum);
2. a positive test for AMA;
3. a liver biopsy with histological evidence of non-suppurative destructive cholangitis and destruction of interlobular bile ducts. Patients who met at least two of the three criteria were included in the study.

Exclusion criteria: alcohol and/or drug dependence, presence of liver cirrhosis class C based on Child Pugh classification, allergic reaction to dairy products, pesence of mental diseases, severe concomitant pathology, regnancy and/or lactation, lactose intolerance.

All patients voluntarily participated in the study, informed consent was signed. The protocol of this study was reviewed and approved by the Local Bioethics Commission. National Scientific Medical Center, Nur-Sultan city, Republic of Kazakhstan. Protocol №051/CT-29.

The age of the patients ranged from 22 to 55 years, the average age was 46.1. The participants are divided into 2 groups. The main group consisted of 14 people; in addition to standard therapy (ursodeoxycholic acid UCDA 15 mg/kg), patients in this group consumed a protein-amino acid and vitamin product (freeze-dried sublimated mares milk, diluted in water) at a dose of 40 g per day during 3 months.

The control group included 9 people; participants in this group received only standard therapy for PBC (ursodeoxycholic acid UCDA 15 mg/kg). Participants from both groups underwent analysis before and after 3 months. Markers of intrahepatic cholestasis were evaluated: gamma-glutamyltranspeptidase (GGT) and alkaline phosphatase (ALP) at the beginning of the study and after 3 months in patients of both groups.

Data processing and research were carried out using analysis of variance based on the Fisher criterion - the F-criterion, and the nonparametric method using the Kruskal-Wallis criterion. The statistical significance of the intragroup

dynamics in the groups of patients — the control and the main, from the time factor — the visit number of patient visits was evaluated.

The level of statistical significance in the comparative analysis was adopted at 0.95 (α = 0.95). It means the expected level of reliability, statistical significance, at which the null hypothesis of the absence of statistical differences in the comparative analysis is rejected, should be less than 0.05 (p <0.05).

Processing was carried out using software products:

• MicrosoftExcel spreadsheet editor for generating tabular data and primary processing of materials, calculating descriptive statistics;

• specialized software StatSoftSTATISTICAforWindows version 6.1 for conducting in-depth statistical analysis, group comparison, building histograms and span diagrams of medium and median.

• Comparison of the dynamics between the groups was carried out in the context of visits using the one-way analysis of variance based on the Fisher criterion - the F-criterion and the non-parametric Kruskal-Wallis test.

The results of the study

In patients of the main group, the level of alkaline phosphatase was significantly reduced to 6.72 ± 0.632 compared with the observation in the control group (9.30 ± 1.553). Comparing the dynamics of the GGT level, in the patients of the main group, this indicator was significantly reduced to 3.88 ± 0.611 compared with the control group (5.53 ± 0.770). Thus, in the main group compared with the control group, a statistically significant dynamics was observed in the studied laboratory indicators of cholestasis.

Below are tables with descriptive statistics (Tables 1-5).

Table 1.

Descriptive statistics for the main group, visit number 1.

№	Indicator	n	Average + standard error	Standard deviation	Confidence Interval for Medium		Median
					-95%	+95%	
1	GGT	14	5,98 ± 1,056	4,479	3,755	8,210	4,32
2	ALP	14	8,20 ± 0,858	3,638	6,389	10,008	6,81

Table 2.

Descriptive statistics for the core group, visit number 2.

№	Indicator	n	Average + standard error	Standard deviation	ConfidenceInterval for Medium		Median
					-95%	+95%	
1	GGT	14	3,88 ± 0,611	2,287	2,557	5,199	3,43
2	ALP	14	6,72 ± 0,632	2,363	5,357	8,086	6,48

Table 3.

Descriptive statistics for the control group, visit number 1.

№	Indicator	n	Average + standard error	Standard deviation	Confidence Interval for Medium		Median
					-95%	+95%	
1	GGT	9	6,22 ± 0,803	3,408	4,527	7,917	5,56
2	ALP	9	8,95 ± 1,147	4,866	6,532	11,371	7,77

Table 4.

Descriptive statistics for the control group, visit number 2.

№	Indicator	n	Average + standard error	Standard deviation	Confidence Interval for Medium		Median
					-95%	+95%	
1	GGT	9	5,53 ± 0,770	2,309	3,752	7,301	6,35
2	ALP	9	9,30 ± 1,553	4,660	5,721	12,884	7,56

Table 5.

A summary table of the results of the assessment of the visit dynamics between the main and control groups using the Kruskal-Wallis test and the Fisher dispersion test (F-test).

Indicator	№ visits	Degrees of freedom	Kruskal-Wallis test	p	Degrees of freedom	F-test	p
GGT	Visit 1	(1;36)	0,4414	0,5064	(1;34)	0,0327	0,8575
	Visit 2	(1;23)	2,8929	0,0890	(1;21)	2,8260	0,1076
ALP	Visit 1	(1;36)	0,1001	0,7517	(1;34)	0,2763	0,6025
	Visit 2	(1;23)	2,0992	0,1474	(1;21)	3,1113	0,0923

As can be seen from figures No. 1, 2 in the main group there was a significant decrease in cholestasis indicators - GGT, ALP.

Discussion

The studied biochemical markers - ALP and GGT - are early markers of cholestasis for establishing the diagnosis of PBC, and are also the main validated indicators for assessing the effectiveness of UDCA therapy and stratifying the risk of disease progression. There are various criteria for evaluating the response to UDCA (Paris, Barcelona, msterdam, Toronto, etc.), but this was not part of the research objectives [4]. Initially, patients with PBC at various stages of the disease (from early to advanced fibrosis) participated in the main and control groups, most of the patients took UDCA preparations for more than 2 years.

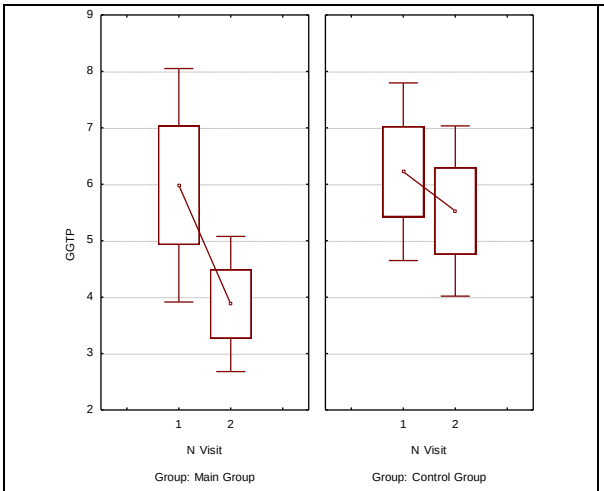

Figure 1. Diagram of the range of means in the context of visits for the GGT indicator

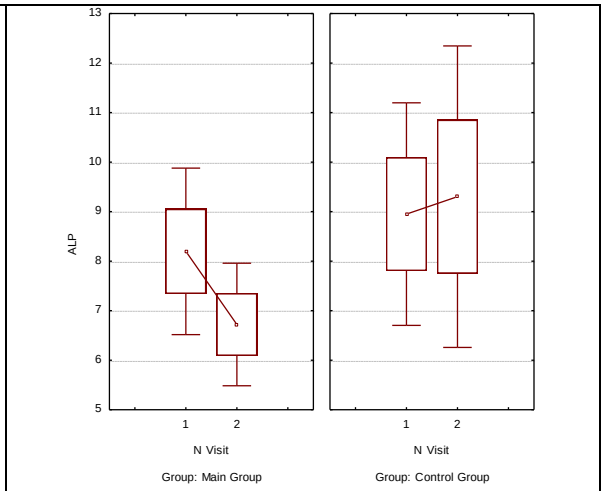

Figure 2. Diagram of the range of average in the context of visits for the indicator ALP.

The study showed a significant decrease in the main markers of intrahepatic cholestasis of ALP and GGT in patients of the main group while taking a complex protein-amino acid and vitamin product (mares milk) as compared with the control group.

In this case, a decrease in cholestasis can be caused not only by the choleretic and cholekinetic effects of the studied product (sublimated mares milk), but also by its indirect effect on the metabolism of bile acids through the intestinal microbiome, exerting a pre- and probiotic effect. According to preliminary data, the majority of patients in the main group who had signs of a constipation syndrome on the background of PBC showed stool normalization, which also influenced an improvement in the quality of life, however, the study of the influence of mares milk on microbiome continues in the framework of this clinical trial.

It is known that pruritus is also one of the main clinical indicators of cholestasis, much worsening the quality of life. This indicator was evaluated on an appropriate scale, but it should be remembered that pruritus is very difficult for an objective assessment. A detailed analysis of the mares milk influence on the intensity of itching (pruritus) and changes in the quality of life is beyond the scope of this study and will be the subject of study in future reports of this ongoing clinical trial (NCT03665519).

During the study, none of the patients in the main group showed any adverse effects while taking the product, and there was no deterioration in the condition and rapid progression (decompensation) of the PBC.

This clinical trial of using mares milk in PBC patients is conducted for the first time in Kazakhstan.

The conclusion. The biochemical response in the form of improved indicators of cholestasis markers (ALP and GGT) is the most validated tool for assessing the effectiveness of treatment of PBC. The study showed a significant decrease in the main markers of intrahepatic cholestasis in patients after taking complex protein-amino acid and vitamin product (mares milk). Thus, the use of freeze-dried mares milk is an effective addition to the standard therapy of PBC.

Conflict of interest. *The authors declare no conflict of interest in this paper.*

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The research results were not published earlier in other publications.

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