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Intrahepatic Cholestasis in Chronic Liver Disease and the Role of Ademetionine in its Treatment (Literature Review and Expert Panel Resolution)

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Aim: to analyse the principles of diagnosis and treatment of intrahepatic cholestasis in chronic liver diseases, to present data on the effectiveness of ademetionine in the treatment of chronic liver diseases with intrahepatic cholestasis and the materials of the Expert Meeting held in 2023.
Key points. During the Expert Meeting, the problems of diagnostics and treatment of intrahepatic cholestasis in various chronic liver diseases were discussed, the effectiveness of ademetionine was clarified, and optimal regimens for its administration were determined.
The relevance of the existing algorithm for diagnosing cholestasis in real clinical practice was assessed. The effectiveness of ademetionine in the treatment of various liver diseases occurring with intrahepatic cholestasis (cholestatic forms of drug-induced liver damage, alcoholic liver disease, non-alcoholic liver disease, primary biliary cholangitis) was demonstrated, manifested by a decrease in clinical and laboratory signs of cholestasis. The anticholestatic mechanisms of ademetionine action were clarified, which consist in normalizing the fluidity of hepatocyte membranes, regulating the activity of Nrf2, a key transcription factor, suppressing lipid peroxidation and the resulting damage to hepatocytes and cholangiocytes. Optimal regimens for prescribing ademetionine for various clinical situations were considered.
Conclusions. Ademetionine is an effective drug that, due to its pleiotropic action and favourable safety profile, can be used in various chronic liver diseases accompanied by cholestasis, including as a part of the complex therapy.
Keywords: intrahepatic cholestasis, chronic liver disease, ademetionine, S-adenosyl-L-methionine
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Внутрипеченочный холестаз при хронических заболеваниях печени и роль адеметионина в его лечении (обзор литературы и резолюция Совета экспертов)

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Цель: проанализировать принципы диагностики и лечения внутрипеченочного холестаза при хронических заболеваниях печени, представить данные об эффективности адеметионина в лечении хронических заболеваний печени с внутрипеченочным холестазом и материалы совещания экспертов, состоявшегося в 2023 г.

Основные положения. В ходе совещания экспертов были обсуждены проблемы диагностики и лечения внутрипеченочного холестаза при различных хронических заболеваниях печени, уточнена эффективность адеметионина, определены оптимальные схемы его приема.
Оценена актуальность существующего алгоритма диагностики холестаза в реальной клинической практике. Продемонстрирована эффективность адеметионина в лечении различных заболеваний печени, протекающих с внутрипеченочным холестазом (холестатические формы лекарственных поражений печени, алкогольная болезнь печени, неалкогольная болезнь печени, первичный билиарный холангит), проявляющаяся уменьшением клинических и лабораторных признаков холестаза. Уточнены антихолестатические механизмы действия адеметионина, которые заключаются в нормализации текучести мембран гепатоцитов, регуляции активности Nrf2, ключевого фактора транскрипции, подавлении перекисного окисления липидов и обусловленного им повреждения гепатоцитов и холангиоцитов. Рассмотрены оптимальные схемы назначения адеметионина для различных клинических ситуаций.
Выводы. Адеметионин является эффективным препаратом, который благодаря плейотропному действию и благоприятному профилю безопасности может применяться при различных хронических заболеваниях печени, сопровождающихся холестазом, в том числе в составе комплексной терапии.
Ключевые слова: внутрипеченочный холестаз, хронические заболевания печени, адеметионин, S-аденозил-L-метионин
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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The Expert Meeting meeting chaired by Professor M.V. Maevskaya was held to address the basic concepts of diagnosing and treating intrahepatic cholestasis (IHC) in various chronic liver diseases (CLDs), as well as the role of ademetionine in its treatment. Professor Maevskaya, who began the Expert Meeting, emphasized its importance due to the increasing prevalence of CLDs with IHC, as well as a lack of awareness of practitioners on use and action mechanisms of various hepatoprotective agents.

Professor E.N. Shirokova (Moscow) stated that CLDs are frequently associated with cholestasis. According to the European Association for the Study of the Liver (EASL), cholestasis is an impairment of bile formation and/or bile flow, which may be asymptomatic or clinically present with fatigue, pruritus, right upper quadrant discomfort, and, in some cases, jaundice. Cholestasis is considered chronic if it lasts for more than 6 months. It is important to remember, that jaundice and cholestasis are not the same, as cholestasis is not always accompanied by jaundice [1, 2].

Cholestasis may be classified as extrahepatic or intrahepatic, depending on the primary anatomic site of the pathology. The latter is classified as hepatocellular and cholangiocellular. Mixed cholestasis is observed in some cases [1, 3]. Table 1 shows the main causes of cholestasis.

It is crucial to understand that IHC can occur in any CLD, regardless of its etiology. It can be observed in the natural course of several CLDs (such as viral hepatitis or non-alcoholic and alcoholic steatohepatitis), with varying incidence and at different stages; however, it often indicates progression and severe course of the diseases [4].

Alkaline phosphatase (ALP) 1.5 times the upper limit of normal (ULN) and gamma-glutamyltransferase (GGT) 3 ULN are considered diagnostically significant [1]. An asymptomatic elevation of ALP may be the first sign of chronic cholestasis. However, in this case, extrahepatic causes of laboratory abnormalities should also be ruled out, since elevated ALP is a common sign of bone diseases. Its hepatic origin is usually suggested by a parallel increase in GGT and/or conjugated bilirubin. However, it should be noted that an isolated increase in ALP with normal GGT occurs in certain liver diseases (for example, progressive IHC types 1 and 2).

The algorithm proposed by EASL (2017) (Fig. 1) should be deemed the most effective for the differential diagnosis of cholestasis. After discussing the algorithm, the experts decided it was appropriate for use by Russian practitioners. The diagnosis will include two stages.

The first stage of the diagnosis is performed by primary care physicians (general practitioners). In case of elevated ALP, GGT, and/or conjugated bilirubin, they should clarify anamnesis and perform physical examination. Test for viral hepatitis, and abdominal ultrasound are required. When questioning the patient, it is necessary to discuss not only the use (especially within 3 months before the onset of cholestasis) of medications, but also various dietary supplements, vitamins, and herbs that can cause drug-induced liver injury (DILI). Moreover, it is necessary to analyze the

Table. Main causes of intrahepatic cholestasis (according to EASL 2012, 2017 with modifications)
Table. Основные причины внутрипеченочного холестаза (по EASL 2012, 2017 с изменениями)

Intrahepatic cholestasis / *Внутрипеченочный холестаз*	
Hepatocellular / *Гепатоцеллюлярный*	**Hepatocellular / *Гепатоцеллюлярный***
· Alcoholic steatohepatitis / *Алкогольный стеатогепатит* · Non-alcoholic steatohepatitis / *Неалкогольный стеатогепатит* · Viral hepatitis / *Вирусный гепатит* · Cholestasis in parenteral nutrition / *Холестаз при парентеральном питании* · Sepsis-, endotoxemia-induced cholestasis / *Сепсис-, эндотоксемия-индуцированный холестаз* · Drug-induced liver injury / *Лекарственные поражения печени* · Genetic diseases (benign recurrent intrahepatic cholestasis type 1–3, progressive familial intrahepatic cholestasis type 1–3, intrahepatic cholestasis of pregnancy, persistent hepatocellular secretory failure, erythropoietic protoporphyria) / *Генетические наследственные заболевания (доброкачественный рецидивирующий внутрипеченочный холестаз 1–3-го типа, прогрессирующий семейный внутрипеченочный холестаз 1–3-го типа, внутрипеченочный холестаз беременных, стойкая гепатоцеллюлярная секреторная недостаточность, эритропоэтическая протопорфирия)* · Benign infiltrative diseases: amyloidosis, sarcoidosis, other granulomatosis, storage diseases / *Доброкачественные инфильтративные поражения: амилоидоз, саркоидоз и другие гранулематозы, болезни накопления* · Malignant infiltrative lesions: in oncohematological diseases, metastases / *Злокачественные инфильтративные поражения: при онкогематологических заболеваниях, метастазах* · Paraneoplastic syndrome (in Hodgkin's lymphoma, renal cell carcinoma) / *Паранеопластический синдром (при лимфоме Ходжкина, почечноклеточном раке)* · Bile duct anomalies / *Пороки желчных протоков* · Nodular regenerative hyperplasia / *Узловая регенераторная гиперплазия* · Vascular disorders (Budd — Chiari syndrome, veno-occlusive disease, congestive hepatopathy) / *Сосудистые нарушения (синдром Бадда — Киари, веноокклюзионная болезнь, застойная гепатопатия)* · Liver cirrhosis (of any etiology) / *Цирроз печени (любой этиологии)*	· Primary biliary cholangitis / *Первичный билиарный холангит* · Primary sclerosing cholangitis / *Первичный склерозирующий холангит* · IgG4-associated sclerosing cholangitis / *IgG4-связанный склерозирующий холангит* · Secondary sclerosing cholangitis (cholangiolithiasis, ischemic, in hereditary hemorrhagic telangiectasia, vasculitis, infectious diseases) / *Вторичные склерозирующие холангиты (холангиолитиаз, ишемические, при наследственной геморрагической телеангиэктазии, васкулитах, инфекционных заболеваниях)* · Drug-induced liver injury / *Лекарственные поражения печени* · Cystic fibrosis / *Муковисцидоз* · Ductal plate malformations: von Meyenberg complexes (biliary hamartomas), Caroli syndrome, congenital liver fibrosis / *Мальформации дуктальной пластинки: комплексы фон Мейенберга (билиарные гамартомы), синдром Кароли, врожденный фиброз печени* · Graft-versus-host disease / *Реакция «трансплантат против хозяина»* · Idiopathic ductopenia / *Идиопатическая дуктопения* · Langerhans cell histiocytosis / *Гистиоцитоз из клеток Лангерганса*

family history to identify possible hereditary diseases. Occupational hazards and previous bile duct surgeries should also be taken into account.

In the majority of cases, abdominal ultrasound helps differentiate between intrahepatic and extrahepatic cholestasis. If the cause of cholestasis cannot be determined, the patient should be referred to a gastroenterologist for the second diagnostic stage with a more thorough assessment (imaging, immunoassay, and genetic screening). Even in the absence of abnormal physical and ultrasound examination findings, regardless of the patient's sex, it is necessary to perform tests for autoantibodies characteristic of primary biliary cholangitis (PBC) (antimitochondrial antibodies, antinuclear factor, anti-sp100 and anti-gp210 antibodies).

Should ultrasound signs of bile duct dilation be detected, magnetic resonance cholangiopancreatography (MRCP) has to be performed, as well as endosonography to visualize the distal zone of the ducts. These tests are also recommended in the absence of anamnestic or ultrasound signs typical for specific diseases during the initial examination.

Liver biopsy is required when serological testing and imaging studies fail to determine the

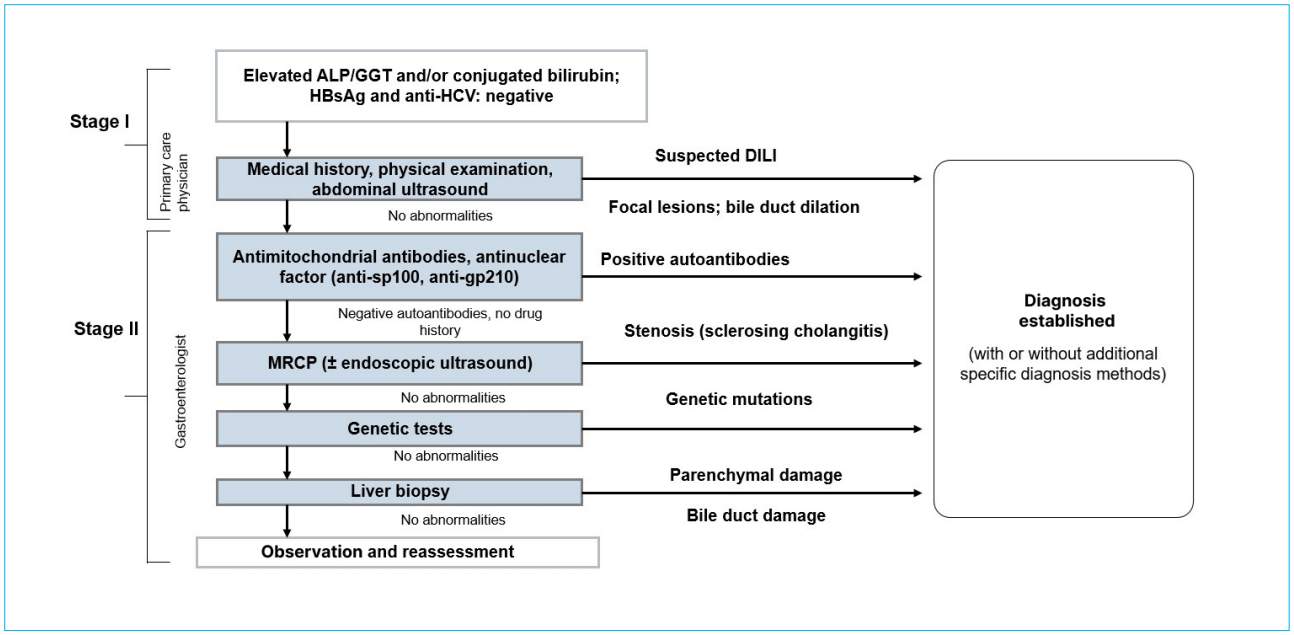

Figure 1. Diagnostic algorithm for chronic cholestasis (according to EASL, 2017 with modifications): ЩФ — alkaline phosphatase, ГГТ — gamma-glutamyl transferase, УЗИ ОБП — ultrasound examination of abdominal organs, МРХПГ — magnetic resonance cholangiopancreatography, эндоУЗИ — endoscopic ultrasound examination

Рисунок 1. Алгоритм диагностики хронического холестаза (по EASL, 2017 с изменениями): ЩФ — щелочная фосфатаза, ГГТ — гамма-глутамилтрансфераза, УЗИ ОБП — ультразвуковое исследование органов брюшной полости, МРХПГ — магнитно-резонансная холангиопанкреатография, эндоУЗИ — эндоскопическое ультразвуковое исследование

cause of cholestasis. It should be noted that liver histology is not always useful in cholestatic diseases. Molecular genetic testing for mutations causing rare monogenic cholestatic syndromes is recommended when other causes of cholestasis are ruled out and the family history, clinical pattern, and examination findings indicate its hereditary nature [1]. If no information can be obtained at this stage of the diagnosis, case follow-up with a subsequent reevaluation of the patient is required.

In her report on DILI, Professor Maevskaya (Moscow) stated, that the pandemic of new coronavirus infection increased the incidence of drug-induced liver injury and drug-induced cholestasis. According to population studies, the incidence of drug-induced liver injury ranges from 2.7 to 19 per 100,000 population per year, with considerable variability in the prevalence and causes of DILI in different parts of the world [5]. More than 1,000 drugs, dietary supplements, and herbal preparations have been identified as contributing to the development of DILI, and this list grows on an annual basis. The drugs that most commonly cause DILI include antineoplastic and antibacterial drugs, non-steroidal anti-inflammatory drugs, psychotropic and lipid-lowering drugs, herbs, and dietary supplements.

Among the adverse drug reactions for DILI, types A and B are the most significant. Type A are predictable, frequent reactions associated with the pharmacological activity of drugs. Type B are unpredictable, dose-independent reactions not associated with the pharmacological activity of drugs (idiosyncrasy). The Council for International Organizations of Medical Sciences (CIOMS) (1999) proposed to classify the types of liver injury (hepatocellular, mixed, cholestatic) based on an increase in ALT or ALP. This classification was further supported by all leading hepatology associations and underlies the diagnosis, differential diagnosis, and treatment of DILI [6, 7].

Cholestatic DILI is frequently associated with polymorphisms in the genes responsible for the activity of glutathione peroxidase (*GPX1Leu*) and manganese superoxide dismutase (*SOD2Ala*), as well as inhibition of bile salt transporters by the multidrug resistance associated protein (MRP) and its fractions (MRP3 and MRP4) [8, 9].

When DILI is suspected, diagnostic algorithm should be based on DILI classification into hepatocellular and cholestatic types (Fig. 2). DILI is diagnosed by assessing the medical history, the potential hepatotoxicity of administered drugs,

and the observed damage phenotype, as well as by ruling out other liver diseases.

To establish the causal relationship between drugs intake and the patient's condition, practitioners must be guided by the RUCAM score, which serves as both professional and legal protection in the future management of the patient [6, 7, 10]. Hy's law is the simplest and most convenient tool for assessing the risk of severe, potentially fatal cases and identifying patients who require urgent hospitalization: jaundice (bilirubin > 2 ULN) in hepatocellular cholestasis (ALT > 3 ULN) suggests a 10 % mortality rate from liver failure [6, 11, 12].

The priority in DILI is to discontinue the drug that caused liver injury. According to Russian and foreign guidelines, depending on the etiology, the DILI phenotype, and the severity of the condition, patients can be prescribed N-acetyl L-cysteine (paracetamol antidote), glucocorticosteroids, L-carnitine, ursodeoxycholic acid (UDCA), and a variety of other medications [6, 7].

The efficacy of ademetionine (S-adenosyl-L-methionine) has been established and proven

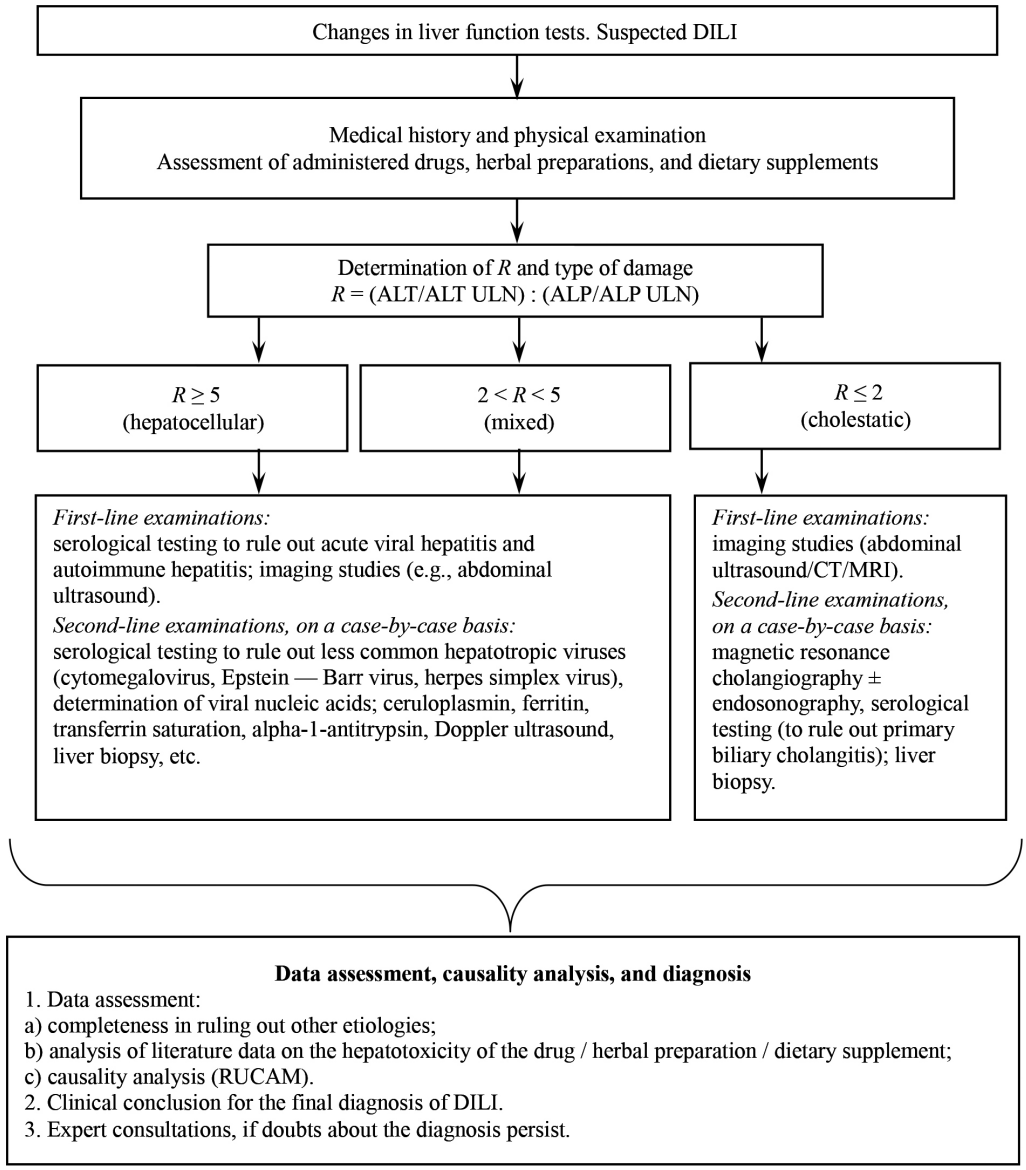

Figure 2. Algorithm of actions in case of suspected drug-induced liver injury (Russian Scientific Liver Society, 2019, with modifications)

Рисунок 2. Алгоритм действий при подозрении на лекарственное поражение печени (Российское общество по изучению печени, 2019, с изменениями)

in a number of clinical studies (CSs) of DILI during anticancer chemotherapy [13, 14]. In cancer patients, it is important to perform anticancer therapy in full and to avoid its delay and discontinuation. When using oxaliplatin-based regimens in patients with colorectal cancer, ademetionine reduces not only the incidence of DILI, but also the need for chemotherapy dose adjustment [15, 16].

In the prospective multicenter study in cancer patients with DILI during polychemotherapy, step therapy with ademetionine (400–800 mg/day parenterally for 2 weeks, then 800–1,600 mg/day orally for 4 weeks) enabled improving clinical and laboratory parameters and performing chemotherapy in full, with better tolerability [17].

Ademetionine has also been shown to be effective in treating cholestatic DILI caused by immunosuppressants in psoriasis [18, 19].

Because of its pleiotropic action, ademetionine in DILI has an anticholestatic effect, providing glutathione and taurine synthesis, bile acid conjugation, and bile acid detoxification, as well as an antineurotoxic and antidepressant effect. Along with the improvement of biochemical parameters, the severity of jaundice, pruritus, and fatigue decreases, and quality of life improves.

Thus, ademetionine should be recommended to patients with specific forms of cholestatic DILI. In severe DILIs requiring treatment with hepatotoxic drugs, step therapy with ademetionine is recommended to accelerate the therapeutic effect.

Professor A.O. Bueverov (Moscow) presented data on the prevalence of ***alcoholic liver disease (ALD)*** in the world and in Russia (8 % of the population), emphasizing that the true prevalence is unknown due to widespread latent alcohol abuse [20, 21]. Among the clinical variants of the disease course, the incidence of cholestatic alcoholic hepatitis is 5–13 % [22]. The most common form of alcoholic hepatitis with jaundice is also accompanied by intracellular cholestasis.

Alcoholic liver disease may be accompanied by IHC due to toxic, mechanical, or inflammatory mechanisms, or a combination of these. Impaired transsulfuration depletes the intracellular pool of thiols and sulfates (glutathione, taurine, etc.) critical for detoxification [23]. The speaker focused on new data on the role of IHC in ALD. Severe alcoholic hepatitis with cholestasis impairs hepatic cell regeneration: due to the deficiency of the hepatocyte nuclear factor HNF-4α, hepatic progenitor cells (oval cells) differentiate into cholangiocytes rather than hepatocytes [24, 25]. A recent study found that in alcoholic hepatitis, the loss of inositol 1,4,5-trisphosphate receptors type 3 on cholangiocytes reflects cholestatic changes at the molecular level; neutrophils bind to β1 integrin on cholangiocytes, which can contribute to the development and persistence of cholestasis [26].

The mechanisms of action of ademetionine in ALD are diverse and complementary, as evidenced by clinical studies [27, 28]. According to G. Vendemiale et al., patients with ALD who received oral ademetionine for 6 months had a significant increase in glutathione in the liver compared to placebo, with a simultaneous decrease in oxidized glutathione and AST [29]. Ademetionine reduces the activity of both cytolysis and cholestasis markers (ALP, GGT), as well as the level of bilirubin, which may indicate an improvement in both cholestasis and hepatocyte function. Laboratory changes are accompanied by a clinical improvement, such as a decrease in jaundice and pruritus [30–33]. A pilot study showed that ademetionine added to classical therapy with prednisolone in severe alcoholic hepatitis reduced the incidence of hepatorenal syndrome. However, the small sample size made it impossible to assess the effect of ademetionine on survival [28]. J.M. Mato et al. demonstrated an increase in the survival rate of patients with alcoholic cirrhosis (Child–Pugh Class A and B) following two years of therapy with ademetionine [34].

Ademetionine has the highest levels of evidence among hepatotropic agents in terms of ALD and is indicated for the treatment of patients with cytolytic and cholestatic syndromes as part of combination therapy [35, 36]. Its efficacy in ALD is determined primarily by the replenishment of glutathione, which is essential for detoxification. Its antioxidant, detoxifying, and antidepressant effects are also significant [37]. Further studies are required to clarify the effect of ademetionine on the survival of patients with severe forms of the disease.

Professor K.L. Raikhelson (Saint Petersburg) emphasized the challenges in the treatment of patients with ***primary biliary cholangitis*** (PBC) due to the growing incidence and prevalence of the disease both in Russia and worldwide [1, 38–40].

UDCA is the basis of PBC therapy; it prevents cirrhosis and reduces the risk of death at all stages of the disease, including in non-responders [41]. It is most effective in patients with a response after one year of treatment [41].

However, there are substantial issues with second-line therapy, in patients who do not respond to UDCA. Obeticholic acid is used as second-line therapy in several countries. However, it has significant side effects (primarily, increased pruritus) and is contraindicated in progressive and decompensated cirrhosis [40].

The efficacy of peroxisome proliferator-activated receptor agonists (fibrates) in PBC was most convincingly demonstrated in the BEZURSO study [42]. Experts currently consider fibrates as an off-label alternative for the treatment of patients with an inadequate response to UDCA; however, they are not recommended for patients with decompensated liver disease [40]. Ongoing phase 3 clinical studies of selective peroxisome proliferator-activated receptor agonists in patients who do not respond to UDCA show promising results [43, 44]. A randomized, placebo-controlled clinical study of the efficacy of budesonide in PBC yielded disappointing results: while improving laboratory parameters, it had no effect on histology parameters [45].

However, even with a response to PBC therapy and a decrease in disease progression, some patients continue to experience persistent pruritus and hepatogenic weakness/fatigue. While UDCA and fibrates reduce cholestatic pruritus, none of the basic PBC therapies (UDCA, obeticholic acid, etc.) has shown any effect on hepatogenic weakness/fatigue [46]. Modafinil seemed promising; however, a double-blind, placebo-controlled, randomized clinical study found it to be ineffective [47].

Several studies have demonstrated the positive effect of ademetionine on laboratory markers and hepatogenic weakness in PBC [48–50]. According to the Polish researchers, patients with PBC who received ademetionine 1,200 mg/day orally for 6 months showed a reduction in hepatogenic weakness/fatigue already after 3 months of therapy, which was maintained after treatment [50]. Further data analysis revealed, that in patients responding to ademetionine treatment, the reduction in hepatogenic weakness was accompanied by a decrease in ALP and antimitochondrial antibodies. The authors suggested that ademetionine has a protective effect on cholangiocytes due to antioxidant properties and replenishment of glutathione deficiency characteristic of chronic cholestasis [50, 51].

Thus, ademetionine is a promising therapy in the complex treatment of PBC, affecting not only laboratory markers of cytolysis and cholestasis, but also hepatogenic weakness/fatigue.

The speaker emphasized on the etiology of chronic secondary IHC, with ***non-alcoholic fatty liver disease (NAFLD)*** as one of its main causes. According to several authors, secondary IHC, which occurs in the natural course of most CLDs, is a marker of severe course, late stages, or specific forms of the disease [52, 53]. This is confirmed by a clinical and morphological study by R. Sorrentino et al., which revealed more severe, total histological hepatic injury with bridging fibrosis or cirrhosis in NAFLD patients with cholestasis and demonstrated a negative effect of cholestasis on disease progression [54]. In steatohepatitis, as compared to steatosis, there is an increase in the periportal ductular reaction, which correlates with the progression of fibrosis [55]. Indeed, depending on the stage of NAFLD, the incidence of histologically confirmed IHC increases from 1/4 of cases with steatosis to almost 1/2 of cases with cirrhosis [56].

In comparison with hepatocellular and mixed patterns, the cholestatic pattern in NAFLD is independently associated with a higher risk of decompensation, hepatocellular cancer, and death from liver diseases [57]. Patients with cholestasis have more pronounced immunohistochemical and histological changes in the liver, including low duct proliferation and biliary metaplasia. Cholestasis is the main predictor of liver-related outcomes in prognostic models [58]. Thus, IHC indicates an unfavorable course of NAFLD.

The positive effect of ademetionine on clinical and biochemical changes in cholestasis in patients with NAFLD has been confirmed in clinical studies [59, 60]. Ademetionine is included in the guidelines for the treatment of NAFLD in adults approved by the Ministry of Health of Russia in 2022, as a treatment of choice, as well as in cases of increased fatigue or in combination of NAFLD and alcoholic injury [61].

I.B. Khlynov, Dr. Sci. (Med.) (Yekaterinburg), reviewed the history of discovery and the ***role of ademetionine molecule***, highlighting the clinical significance of methionine adenosyltransferase (MAT) involved in the synthesis of ademetionine [62].

Ademetionine is primarily synthesized in the liver, where more than 50 % of daily methionine intake is metabolized and 85 % of methylation reactions take place, which determine membrane integrity and metabolism of lipids and neurotransmitters. This explains the positive effect of ademetionine on cytolysis. The participation of ademetionine in transsulfuration reactions improves bile secretion, inhibits apoptosis in the liver tissue during aminopropylation reactions in inflammatory liver diseases, stimulates liver regeneration, and has an antifibrotic effect [63, 64].

Experimental studies in murine models demonstrated that MAT inhibition accompanied by impaired ademetionine synthesis results in steatohepatitis, followed by hepatocellular carcinoma [65]. In contrast, replacement therapy with ademetionine decreases cytolysis and improves liver histology, preventing steatohepatitis [66].

Decreased *MAT* gene expression in patients with liver fibrosis was observed in two independent clinical studies in patients with non-alcoholic

steatohepatitis. The severity of fibrosis correlated with the deficiency of the enzyme that catalyzes the synthesis of ademetionine, confirming the relevance of replacement therapy with ademetionine rather than its precursor methionine in patients with CLD [67, 68].

The main anticholestatic mechanisms of ademetionine are discussed in detail and systematized in the literature review by V.T. Ivashkin and A.O. Bueverov. These include improved fluidity of hepatocyte membranes, suppression of lipid peroxidation, including through regulation of the key transcription factor activity, and modification of bile acid transport [69].

In the part of the report addressing ***main patient profiles and ademetionine therapy regimens***, Igor B. Khlynov cited several non-randomized and randomized clinical studies that showed the efficacy of ademetionine in a wide range of diseases accompanied by IHC, including ALD, DILI, NAFLD, and viral hepatitis [19, 32, 48, 59, 70–74]. The primary outcomes of ademetionine therapy in all these clinical studies were a decrease in biochemical markers of cytolysis and cholestasis, as well as efficacy against weakness/fatigue, the main symptom of CLD. A systematic review and meta-analysis by M. Noureddin et al. (2020) confirmed that in various CLDs with cholestasis, a significant improvement in symptoms and laboratory markers of liver injury was observed after 2 weeks of treatment with ademetionine, with further improvement after 4 and 8 weeks of treatment [75]. V.T. Ivashkin et al. demonstrated the optimal regimen of ademetionine therapy and the efficacy of switching from its parenteral form to the oral form in real-world clinical practice [32].

When selecting an initial therapy, a higher bioavailability of parenteral ademetionine (up to 80–90 %) should be taken into account. Oral ademetionine has a topical effect due to the first-pass effect and rapid metabolism of ademetionine in the liver [76].

Ademetionine studies used a variety of doses, routes of administration, and treatment durations. The speaker discussed in detail the selection of treatment regimens and the criteria to be followed by practitioners. He proposed identifying the most common profiles of IHC patients who can benefit from ademetionine: patients with ALD and cholestasis, cholestatic DILI, NAFLD, and complicated IHC.

It is advisable to consider two options for initial therapy. Patients with CLD and IHC in satisfactory condition, with a favorable short-term prognosis or short-term improvement, requiring outpatient treatment, should receive ademetionine at a dose of 10–25 mg/kg/day orally, depending on the severity of the disease. In inpatient settings (including day hospitals), step therapy is recommended to patients with symptomatic IHC, moderate or severe disease, or an uncertain long-term prognosis: ademetionine 5–12 mg/kg/day parenterally for 2 weeks, with subsequent switching to oral ademetionine.

The speaker focused on the duration of ademetionine therapy and proposed the degree of fibrosis according to elastometry as a time criterion: in patients with CLD, IHC, and Grade 0–1 fibrosis, the duration of ademetionine therapy can be 8 weeks or more (until an improvement in cytolysis and cholestasis markers); in patients with Grade 2–4 fibrosis, the duration of therapy should be at least 24 weeks. During the discussion, several experts expressed doubts that elastometry findings are a reasonable parameter of choice for determining the duration of therapy. First, elastometry is not available in all healthcare facilities. Second, the liver stiffness measured by elastometry results from a combination of factors, including not just the severity of fibrosis but also, for example, inflammatory activity. Thus, its correct interpretation can be difficult.

The use of ademetionine during pregnancy was also addressed. The experts emphasized that ademetionine is only allowed during the third trimester of pregnancy, according to the prescribing information. It can be used to enhance the effect of UDCA in cholestasis of pregnancy [77] and in other cases of IHC. In the first and second trimesters, ademetionine can be used following a case conference, when the benefits of therapy outweigh the risks. The duration of therapy is determined on a case-by-case basis by an obstetrician-gynecologist and a gastroenterologist (or a general practitioner); case follow-up is required [78].

Ademetionine is included in the current Russian guidelines (https://cr.minzdrav.gov.ru) for several diseases (ALD, NAFLD, DILI), which justifies its use in secondary IHC associated with these diseases.

Following a detailed discussion of the presented reports, the resolution was adopted that included the following key points.

1. The EASL (2017) cholestasis criteria and diagnostic algorithm should be used in clinical practice for the diagnosis and differential diagnosis of cholestasis.

2. The efficacy of ademetionine in intrahepatic cholestasis is determined by its anticholestatic mechanisms, including improved fluidity of hepatocyte membranes, regulation of Nrf2 (a key transcription factor) activity, replenishment of glutathione, and suppression of lipid peroxidation

and associated damage to hepatocytes and cholangiocytes.

3. Clinical studies, including those with level of evidence I (A) and II (B), demonstrated the efficacy of the original ademetionine in various chronic liver diseases in reducing the severity of clinical symptoms of cholestasis (pruritus, fatigue) and laboratory markers of liver injury (activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, bilirubin level).

4. Because of its pleiotropic action and favorable safety profile, ademetionine can be used in various chronic liver diseases with intrahepatic cholestasis.

5. Experts recommend ademetionine for the treatment of diseases with secondary intrahepatic cholestasis: in alcoholic liver disease with intrahepatic cholestasis, wcholestatic type of drug-induced liver injury, non-alcoholic fatty liver disease with the development of intrahepatic cholestasis.

6. The regimen of ademetionine therapy is selected by the physician, considering the patient's characteristics, including the etiology and stage of the disease, comorbidities, concomitant therapy, and body weight. High doses and longer duration of therapy increase the efficacy of ademetionine.

7. The regimen of ademetionine therapy should be selected as follows:

– in patients with intrahepatic cholestasis without significant clinical manifestations: outpatient treatment, up to 1,600 mg/day orally for 1 month or more;

– in patients with intrahepatic cholestasis with severe clinical manifestations – inpatient treatment; in cases requiring a rapid response to therapy (for example, drug-induced liver injury) – step therapy, 400–800 mg IV or IM for 2 weeks, with subsequent switching to oral form up to 1,600 mg/day;

– in the absence of fibrosis, the duration of treatment is determined by clinical symptoms and the level and rate of improvement in laboratory markers of the liver, and can be 4 weeks, 8 weeks, or more;

– in advanced stages of fibrosis, the duration of therapy should be at least 24 weeks; the maximum duration is not limited;

– in alcoholic cirrhosis (Child – Pugh Class A and B), the duration of therapy should be at least 2 years, at a dose of at least 1,200 mg/day.

8. Ademetionine can be used for the treatment of intrahepatic cholestasis in pregnant women in the third trimester.

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