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DRUG-INDUCED LIVER DAMAGE. CLINICAL CASE

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Drug-induced liver damage is one of the formidable liver diseases that can appear in the practice of every doctor after the appointment of treatment and lead to a fatal outcome. The described clinical case demonstrates hepatitis that developed against the background of taking basic drugs for the underlying disease. This article describes the course and severity of the disease, the dynamics of the increase in symptoms.

In recent years, the prevalence of drug-induced hepatitis of various etiologies has been growing. The data provided in the article will be useful to therapists, general practitioners, gastroenterologists and rheumatologists.

Key words: *drug-induced liver damage, drug-induced hepatitis, basic therapy, rheumatoid arthritis.*

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Резюме

ЛЕКАРСТВЕННО-ИНДУЦИРОВАННОЕ ПОРАЖЕНИЕ ПЕЧЕНИ. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Лекарственно-индуцированное поражение печени является одним из грозных заболеваний печени, который может появиться в практике каждого врача после назначения лечения и привести к летальному исходу. Описанный клинический случай демонстрирует гепатит, который развился на фоне приема базисных препаратов основного заболевания. В данной статье описывается течение и тяжесть заболевания, динамика нарастания симптомов.

За последние годы распространённость лекарственно-индуцированного гепатита разной этиологии растет. Данные, приведенные в статье, будут полезны терапевтам, врачам общей практики, гастроэнтерологам и ревматологам.

Ключевые слова: *лекарственно-индуцированное поражение печени, лекарственно-индуцированный гепатит, базисная терапия, ревматоидный артрит.*

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Түйіндеме

БАУЫРДЫҢ ДӘРІМЕН ИНДУЦИЯЛАНҒАН ЗАҚЫМДАЛУЫ. КЛИНИКАЛЫҚ ОҚИҒА

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Бауырдың дәрімен индуцияланған зақымдалуы бауыр ауруларының қауіпті аурулардың бірі және әр дәрігердің тәжірибесінде дәрілік заттардың тағайындағаннан кейін пайда болатын, сонымен қатар пациенттің өліміне әкелетін ауру. Баяндалған клиникалық оқиға негізгі аурудің базисті препараттарын қабылдаған кезде пайда болған гепатит оқиғасы көрсетілген. Бұл мақалада ауру ағымының ауырлығы, симптомдардың өсу динамикасы, клиникалық суреттің ағымы келтіріледі.

Соңғы жылдары әртүрлі этиологиялы дәрімен индуцияланған гепатит таралуы артуда. Бұл мақалада келтірілген мәліметтер терапевттерге, жалпы тәжірибе дәрігерлеріне, гастроэнтерологтарға және ревматологтарға пайдалы болады.

Түйінді сөздер: *бауырдың дәрімен индуцияланған зақымдалуы, дәрімен индуцияланған гепатит, базисті терапия, ревматоидты артрит.*

Дәйексөз үшін:

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Introduction.

The rise of drug-induced liver injury (DILI) in the modern world is a consequence of the growing number of prescriptions and the range of available drugs, despite the growing awareness of hepatotoxicity and the availability of less toxic alternatives, the absolute frequency of hepatic reactions to drugs has not decreased [1,2]. The majority of drug-induced hepatotoxicity occurs in an unpredictable manner when the drug is used as recommended, which defines an idiosyncratic event [3].

Acute liver failure (ALF) due to DILI is rare but is a concern for both physicians and patients. A prospective study used detailed case report forms in 1,198 patients enrolled at 23 centers in the United States (US), all of whom had received liver transplantation [4].

A total of 133 (11.1%) patients with ALF were considered to be due to DILI; 81.1% were considered very likely, 15.0% likely, and 3.8% possible. The authors state that ALF due to DILI develops slowly, is more common in women, and rarely shows spontaneous recovery, but transplantation provides excellent survival [4]. Another study found that acetaminophen toxicity was the most common cause in patients with ALF in Sweden [5]. Japanese researchers studied the characteristics of fulminant liver failure of non-viral and drug-induced aetiology [6], their results showed that the latency period of the disease and the peak level of total bilirubin may be prognostic factors for the severity of drug-induced fulminant liver failure. When studying the etiology of ALF due to DILI, it was found that in European [5,7] and US [4,8] countries, drugs were the main causes of ALF. Whereas in Asian countries, traditional biological and dietary supplements were the main causes of DILI [9].

Objective: to describe a case of drug-induced liver damage, which may occur in daily practice of a doctor and to present modern methods of diagnostics of this disease.

Materials and Methods:

The patient's medical history was analysed - a patient, 58 years old, who was on inpatient treatment in the Cardio-Rheumatology Department of the University Hospital (UH) of Semey Medical University (SMU) NJSC during the period from 17.01.2025 to 31.01.2025. In describing the case, we used data from the medical records of the inpatient.

The patient is admitted to the cardio-rheumatological department in a planned procedure. Complaints on admission: pain in knee, shoulder wrist joints, small joints of the feet, cervical spine, pain and swelling in small joints of the hands, morning stiffness before lunch, restriction of movement due to pain, deformity of the joints of the hands. According to the patient's words, these manifestations have been bothering him since 2018, when signs of arthritis of the joints of the hands with further involvement of other joints appeared. He first went to a rheumatologist in 2020 and was diagnosed with rheumatoid arthritis (RA). In 2020

he received 3 injections of Metoject 12.5 mg/week. After the patient cancelled the drug on his own due to intolerance, as nausea and abdominal pain appeared. At present, he regularly takes Metipred 4 mg/day, vitamin D, calcium. The last inpatient admission to the cardioreumatology department of the UH SMU NJSC was in November 2024. After discharge from the hospital, it was recommended to gradually reduce the dose of Metipred from 4 mg/day to complete withdrawal under the supervision of the rheumatologist in the place of residence. It was also recommended baseline therapy with Metoject according to the increasing scheme up to 17.5 mg/week subcutaneously. But taking into account poor tolerability of Metoject and high RA activity, genetically engineered biological targeting therapy with Golimumab (Simpani) 50 mg once a month was suggested. At the end of December received 1 injection of Metoject 15 mg/week, folacin 5 mg after 24 hours. This worsening of condition during 2 weeks with intensification of joint syndrome symptoms. As there was no improvement of the condition, I applied to the polyclinic at the place of residence. The drug Golimumab (Simpani) 50 mg for a single subcutaneous injection was available. Given the pronounced signs of joint syndrome, inflammatory and astheno-vegetative syndromes, he was hospitalised on a planned basis in the Department of Cardio-Rheumatology of the UG SMU NJSC for correction of therapy and improvement of the quality of life.

Past medical history: The patient grew and developed according to his age. He denies tuberculosis, venereal diseases. From the transferred diseases notes arterial hypertension and acute cerebral circulation disorder in 2024, received inpatient treatment from 11.12.2024 to 19.12.2024 in the cardiology department of the Emergency Hospital of Semey city with the diagnosis: Acute cerebral circulation disorder. Ischaemic stroke in the cortical branches of the left middle cerebral artery basin (atherothrombotic). Right-sided hemisyndrome. Arterial hypertension, grade 2 risk 4. Regularly he takes thrombopol. Underwent operations for inguinal hernia in 1983 and in 1985. No haemotransfusions have been performed. Heredity is not aggravated. He denies contact with infectious patients. The epidemiological environment is clean. Allergological anamnesis is not aggravated.

Objective data:

The general condition was assessed as average due to the main disease - RA. Consciousness is preserved, clear. Answers questions clearly, concentration of attention is preserved. Psychoemotional background is stable. Correct physique, moderate nutrition. Skin is dry, clean, normal colour. Skin turgor is preserved. There are postoperative scars on the anterior surface of the abdomen after the operation for inguinal hernia. Peripheral lymph nodes are not palpated. There are no peripheral oedemas. The chest is normosthenic, symmetrical on both sides, participates in the act of breathing on both sides. Frequency of respiratory movements - 18 times per minute. Vocal tremor is equally conducted on both sides. At auscultation of lungs - vesicular breathing, no rales. When examining the heart area, no pathological pulsations are seen. On palpation of the heart, the apical thrust is determined in the fifth intercostal space along the midclavicular line. On percussion of the heart, the right border of relative cardiac dullness is located in the fourth intercostal space 1 cm outside the right edge of the sternum. The left border of relative cardiac dullness is located in the fifth intercostal space along the middle clavicular line on the left, and the upper border of relative cardiac dullness was determined along the upper edge of the 3rd rib 1 cm outside of the sternoclavicular junction on the left. On auscultation of the heart, cardiac tones were muffled, rhythmic. The rhythm was sinus. Heart rate was 80 beats per minute. Pulse was 80 beats per minute. Blood pressure was 110/70 mmHg. At auscultation of vessels no noise symptoms were detected. The tongue was moist and covered with white plaque. The volume of the abdomen was not increased, soft. On the anterior surface of the abdomen there was a postoperative scar after the operation for inguinal hernia. On palpation the abdomen was painless, soft. On percussion of the abdomen, the lower edge of the liver did not extend beyond the edge of the rib arch. On palpation the liver is not enlarged, it is located at the edge of the rib arch, the lower edge is sharp, smooth, painless. At percussion of the spleen the size is not enlarged, at palpation the spleen is not palpated. Stools were clear without pathological impurities once in 1-2 days. The kidney area was unchanged. Urination was free, painless. The palpation symptom was negative on both sides.

20.01.2025 General blood analysis on the analyzer with differentiation of 5 classes of cells: leukocytes – 7.56 10^9/L; erythrocytes – 4.58 10^{12}/L; hemoglobin - 137 g/l; hematocrit – 40.4%; platelets - 262 10^9/L; mean hemoglobin per cell - 29.8 pg; relative platelet volume - 0.205%; Coefficient of variation of erythrocytes - 14.9%; Relative neutrophils - 59.8%; Absolute neutrophils - 4.52 10^9/L; Platelet volume distribution width - 15.5%; Monocyte count - 0.31 10^9/L; Relative monocytes - 4.1%; Absolute eosinophil - 0.30 10^9/L; Relative eosinophil - 3.9%; Absolute basophils - 0.04 10^9/L; relative basophils - 0.6%; absolute lymphocytes - 2.39 10^9/L; relative lymphocytes - 31.6%; Measurement of erythrocyte sedimentation rate (ESR) in blood on the analyzer - 24 mm/hour.

20.01. 2025 Biochemical analysis of blood serum on analyzer: C Reactive protein (CRP) - 22.1 mg/L; Alanine aminotransferase (ALT) - 147.9 U/L; Aspartate aminotransferase (AST) - 125.1 U/L; Glucose - 4.42 mmol/L; Creatinine - 72.0 μmol/L; Urea - 3.99 mmol/L; Uric acid - 273.8 umol/L; Total protein - 69.33 g/L; Total bilirubin - 8.42 μmol/L; Total cholesterol - 5.1 mmol/L; Direct bilirubin - 2.64 μmol/L.

20.01.2025 Coagulogram: Prothrombin time, 10.61 seconds; Prothrombin index (PTI), 108.50%; International normalized ratio (INR), 0.89; Thrombin time, 15.38 seconds; fibrinogen, 4.15 g/L.

20.01.2025 Investigation of the general analysis of urine on the analyser (physico-chemical properties with counting the number of cellular elements of urine sediment): relative density - 1010; pH (acidity in urine) - 6; leukocytes in urine - 6-7 cells/μl; colour - yellow; Transparency of urine - transparent; Mucus - +.

22.01.2025 Biochemical analysis of blood serum on the analyzer: ALT – 294.3 U/L; AST – 169.9 U/L.

24.01.2025 General blood analysis on the analyzer with differentiation of 5 classes of cells: leukocytes – 8.08 10^9/L; erythrocytes – 4.74 10^{12}/L; hemoglobin - 141 g/l; hematocrit – 42.2 %; platelets - 276 10^9/L; mean hemoglobin per cell -

29.9 pg; relative platelet volume - 0.218%; Coefficient of variation of red blood cells - 14.5%; Relative neutrophils - 46.7%; Absolute neutrophils - 3.78 10^9/L; Platelet volume distribution width - 15.5%; Monocyte count - 0.51 10^9/L; Relative monocytes - 6.4%; Absolute eosinophil - 0.49 10^9/L; relative eosinophil, 6.2%; absolute basophils, 0.06 10^9/L; relative basophils, 0.7%; absolute lymphocytes, 3.24 10^9/L; relative lymphocytes, 40%; ESR, 14 mm/hour;

27.01.2025 Biochemical analysis of blood serum on the analyzer: ALT - 342.5 U/L; AST - 219.9 U/L.

28.01.2025 General blood analysis on the analyzer with differentiation of 5 cell classes: leukocytes - 7.93 10^9/L; red blood cells - 4.95 10^{12}/L; hemoglobin - 148 g/l; hematocrit - 43.5%; platelets - 328 10^9/L; average value of hemoglobin per cell - 29. 8 pg; relative platelet volume - 0.260%; Erythrocyte coefficient of variation - 14.9%; Relative neutrophils - 42.3%; Absolute neutrophils - 3.35 10^9/L; Platelet volume distribution width - 15.4%; Monocyte count - 0.40 10^9/L; relative monocytes - 5.0%; absolute eosinophil - 0.35 10^9/L; relative eosinophil - 4.4%; absolute basophils - 0.04 10^9/L; relative basophils - 0.5%; absolute lymphocytes - 3.79 10^9/L; relative lymphocytes - 47.8%; COE - 5 mm/hour;

28.01. 2025 Biochemical analysis of blood serum on the analyzer: ALT - 382.6 U/l; AST - 224.5 U/l; GGTP - 95.5 U/l; creatinine - 73.4 μmol/l; urea - 4.99 mmol/l; total protein - 75.79 g/l; total bilirubin - 11.43 μmol/l; total alpha-amylase - 65.1 U/l; direct bilirubin - 2.91 μmol/l; Rheumofactor (RF) (quantitative) - >500 IU/ml; alkaline phosphatase - 93.6 U/l.

Table 1.

Dynamics of the results of a general blood test.

Complete blood count	Hemoglobin, g/l	Erythrocytes, 10^{12}/l	Leukocytes, 10^9/l	Platelets, 10^9/l	ESR, mm/h
26.11.2024	140	4.73	9.95	307	33
28.11.2024	135	4.55	11.67	307	41
20.01.2025	137	4.58	7.56	262	24
24.01.2025	141	4.74	8.08	276	14
28.01.2025	148	4.95	7.93	328	5
ESR – erythrocyte sedimentation rate;					

Table 2.

Dynamics of biochemical blood test results.

Blood biochemistry	ALT IU/L	AST, IU/L	Total bilirubin, μmol/L	Direct bilirubin, μmol/L	Total cholesterol, mmol\L	RF, IU/L	Total protein, g/L	CRP mg/L	GGT, U/L	Alkaline phosphatase, IU/L	Creatinine μmol/L	Urea mmol/L
26.11.2014	23.8	25.4	6.37	2.11	-	334.59	66.68	15.69	-	-	62.5	5.7
20.01.2025	147.9	125.1	8.42	2.64	5.1	-	69.33	22.1	-	-	72	3.99
22.01.2025	294.3	169.9	-	-	-	-	-	-	-	-	-	-
27.01.2025	342.5	219.9	-	-	-	-	-	-	-	-	-	-
28.01.2025	382.6	224.5	11.43	2.91		500	75.79		95.5	93.6	73.4	4.99
ALT - alanine aminotransferase; AST - aspartate aminotransferase; RF - rheumatoid factor; CRP - C-reactive protein; GGT - gamma-glutamyl transpeptidase;												

Table 3.

Dynamics of blood coagulogram results.

Coagulogram	APTT, sec	Klaus-fibrinogen, g/l	SFMC, mg/100 ml	Thrombin time, sec	Prothrombin time, sec	INR	PTI %
26.11.24	21.49	4.23	-	14.16	11.4	0.95	97.64
20.01.25	-	4.15	-	15.38	10.61	0.89	108.5
APTT – activated partial thromboplastin time; SFMC – soluble fibrin-monomer complexes; INR – International Normalized Ratio; PTI – prothrombin index							

28.01.2025 Study of the general analysis of urine on the analyzer (physic-chemical properties with counting the number of cellular elements of the urine sediment): relative density - 1020; glucose - negative; protein - negative; pH (acidity in the urine) - 6.0; erythrocytes in the urine - 0-2 cells/μl; leukocytes in the urine - 5-6 cells/μl; colour - yellow; Transparency of urine - transparent; Mucus +.

25.11.2024 Radiography of the hand with grasping of the wrist joint. Conclusion: Rheumatoid arthritis of the hands, 2nd degree combined with osteoarthritis.

25.11.2024 Radiography of the foot. Conclusion: Rheumatoid arthritis of small joints of the feet, 2nd degree.

25.11.2024 X-ray review of the chest organs (1 projection). Conclusion: No infiltrative changes in the lungs.

25.11.2024 Complex ultrasound diagnostics (liver, gallbladder, pancreas, spleen, kidneys). Conclusion: Ultrasound signs of diffuse changes in the liver parenchyma. Chronic cholecystitis. Diffuse changes in the pancreas parenchyma by type of chronic pancreatitis. Thickening and deformations of the calyx-lochanous composition of the kidneys, chronic pyelonephritis, micronephrolithiasis.

17.01.2025 Radiography of the cervical spine Conclusion: Spondylosis of the cervical spine, 2nd degree. Spondyloarthrosis.

17.01.2025 Echocardiography. Conclusion: Cardiac cavity dimensions are not dilated. Hypertrophy of myocardial walls of the left ventricle. Aortic wall and aortic

valve (AC) and mitral valve (MV) flaps thickening. Calcinosis of aortic root and aortic and mitral valve flaps - I degree. Diastolic function of the left ventricular myocardium is disturbed by type 1. Mitral regurgitation +. Separation of pericardial epicardial sheets 4 mm wide (about 60 ml). Systolic function of the left ventricular myocardium is satisfactory. The ejection fraction is 64%.

28.01.2025 Ultrasound of hepatobiliopancreatic region (liver, gallbladder, pancreas, spleen) Conclusion: Additional features: Visualisation is difficult due to pronounced flatulence. Severe flatulence. Conclusion: Ultrasound signs: diffuse changes of liver parenchyma, chronic cholecystitis, diffuse changes of pancreas parenchyma by type of chronic pancreatitis.

17.01.2025 Consultation: Physiotherapist Conclusion: Physiotherapy, Massage No. 5

22.01.2025 Consultation: Neurologist Conclusion: Diagnosis: Cervical dorsopathy, cervicalgia on the background of muscular-tonic syndrome.

Recommended:

1. NSAIDs (Lornoxicam or Naiz.)
2. Muscomed 2.0 v/m 2 p/d - 3 days
3. Massage on the cervical-collar zone in the absence of contraindications.
4. Observation at the neurologist at the place of residence, Magnetic resonance imaging of the cervical spine on an outpatient basis
5. Avoid hypothermia, sharp movements of the cervical spine.

28.01.2025 Consultation: Gastroenterologist Conclusion: Diagnosis: Drug-induced liver damage (methotrexate + simpani), hepatocellular type (ALT above 8 upper limit of normal). Chronic non-calculous cholecystitis, remission. Chronic pancreatitis, remission.

Recommended:

1. Ultrasound examination of abdominal cavity organs;
2. GGTP, alkaline phosphatase, bilirubin with fractions, total cholesterol, total protein with fractions, INR, PTI;
3. PCR for viral hepatitis B and C;
4. Exclude the use of dietary supplements and multivitamins without a doctor's prescription, a conversation was held;
5. Hospitalisation in the Department of Gastroenterology through the portal.

Therapy performed in the Cardio-Rheumatology Department:

Diet: 15 Regimen: 2b - ward, Ketorosan, Omegast, Pyridoxine hydrochloride, Cyanocobalamin, Pentoxifylline, Simponi, Metodect, Heptral, Muscomed, Magnetotherapy, Electrophoresis, Massage of neck, collar area and both shoulder joints.

Discussion

The diagnosis of DILI is made after excluding other etiological liver lesions such as, virus, alcohol, toxins, autoimmune liver injury, ischaemia etc. [10]. This clinical case clearly showed that DILI can develop even with standard doses of treatment of the underlying disease. Along with this, we would like to remind that always when prescribing any drugs, it is necessary to take into account their toxicity to internal organs and side effects that they may cause even at standard recommended doses. The peculiarity of this clinical case is that DILI developed rapidly within a month after the start of treatment and timely detection of the initial symptoms of this liver damage will prevent the development of liver failure.

Information about possible side effects of medicines and mechanisms of side effects after taking medicines can be found in certain DILI registries, which are freely available on the Internet. For example, these are LiverTox, The Spanish DILI registry, US DILIN, LATINDILIN, and others.

With the aim of early detection of patients with DILI, a co-operative network 'The Spanish DILI registry' was established in Spain in 1994 [11]. The results of this registry revealed that antibiotics caused the most common type of liver damage, which was inversely proportional to age and had the worst outcome [11]. Various clinical, pharmacological and genetic aspects of DILI have also been identified.

Another registry, US DILIN, established in 2004 and funded by the US National Institutes of Health, is an ongoing observational study of both children over 2 years of age and adults with suspected DILI [1,12]. There is also the Latin American DILI Network (LATINDILIN), which aims to prospectively identify true cases of LIPP and collect biological samples for genetic biomarker studies [13].

One useful resource that clinicians should be aware of is LiverTox (https://www.ncbi.nlm.nih.gov/books/NBK547852/), which has information on up-to-date, unbiased, and accessible reports and articles on the diagnosis, cause, incidence, clinical patterns, and treatment of liver damage caused by prescription, over-the-counter drugs, and selected herbal products. For this patient, we applied this resource, which showed methotrexate causes an increase in serum aminotransferase levels, and long-term therapy is associated with the development of fatty liver disease, fibrosis, and even cirrhosis. When high doses of methotrexate are administered intravenously, serum ALT levels may rise 10-20 times above the upper limit of normal (ULN) for 12-48 hours, but then levels fall rapidly to normal, and only rarely do jaundice or symptoms of liver damage occur, as was observed in our patient.

LiverTox recommends monitoring serum aminotransferase levels with methotrexate therapy monthly for at least 6 months and then every 3 months, with more intensive monitoring and withdrawal of therapy if aminotransferase levels increase and remain above 3 times the ULN. Whereas, in our patient, ALT levels rose above 7 times the ULN and AST levels rose to 4 times the ULN within a month of receiving the first methotrexate injection.

Golimumab is a human monoclonal antibody to tumor necrosis factor (TNF) alpha that is used in the treatment of rheumatoid arthritis and ulcerative colitis (https://www.ncbi.nlm.nih.gov/books/NBK547852/). Golimumab rarely causes elevation of serum enzyme levels during therapy, but may cause reactivation of chronic hepatitis B in susceptible patients.

There are several factors that influence the development of DILI, such as age, gender, ethnicity, alcohol consumption, and comorbidities. According to some studies, the incidence of serious adverse drug reactions increases with age [14], this may be related to the dose of medication taken, as drug excretion decreases with age. The effect of age on the incidence of DILI may be due to the fact that patients take more medication as they age [15].

A high risk of adverse drug reactions is more common in female patients compared with male patients. Women

appear to be more susceptible than men to fulminant liver failure/ALF, especially in response to some anti-infective drugs and to autoimmune hepatitis following exposure to some other drugs [16].

The influence of ethnicity on an individual's response to medications is primarily due to differences in single nucleotide polymorphisms among people from different ethnic groups [3]. In a cohort study, the authors found that trimethoprim/sulfamethoxazole, methyldopa, and phenytoin were more likely to cause DILI among African Americans, whereas amoxicillin-clavulanate was the causative agent in significantly more Caucasians [17]. Although these differences may be related to genetic factors, equally, factors such as the indications for these drugs, as well as differences in prescribing patterns, may explain the difference between different groups [17].

Alcohol consumption has been included as a risk factor for DILI because alcohol is a recognised inducer of CYP2E1 and, as such, is crucial in the formation of N-acetyl-rbenzoquinonimine, the reactive metabolite responsible for acetaminophen hepatotoxicity [18]. However, data supporting alcohol as a risk factor for idiosyncratic DILI are only available for selected drugs such as isoniazid, methotrexate and halothane [19]. Also in the DILIN cohort, any alcohol consumption in the previous 12 months was a negative predictor of severe DILI [12].

The high risk of development in the elderly may also be related to comorbidity, i.e. co-morbidities and increased drug exposure, which may influence susceptibility to hepatotoxicity [3]. Drugs are also known to act synergistically with other risk factors, contributing to the pathogenesis and progression of drug-related fatty liver disease [3].

In a multicenter study involving more than 5000 women, tamoxifen therapy was associated with a 2-fold risk of developing fatty liver disease over a 5-year period, with an incidence of 0.4% per year in the treated group compared with 0.2% in the placebo group [20]. This association was often seen in overweight and obese women, and the increased risk of developing fatty liver disease was evident during the first 2 years of treatment. Other factors associated with the development of fatty liver disease included hypercholesterolemia and arterial hypertension. In a breast cancer registry, the likelihood of developing nonalcoholic steatohepatitis increased 8.2-fold when patients were treated with tamoxifen, and most had normalized liver enzymes after discontinuation of tamoxifen [21]. In addition, the likelihood of non-alcoholic steatohepatitis increased by 13% for every 1 kg/m2 increase in body mass index and decreased by 5% for every 1 year increase in age [21].

The most dangerous side effect of long-term methotrexate treatment is liver steatosis and fibrosis [22]. The presence of type 2 diabetes mellitus, overweight, excessive alcohol consumption and chronic hepatitis B or C in psoriasis patients treated with methotrexate increased the risk of liver fibrosis [23]. The authors stated that psoriasis patients treated with methotrexate who had risk factors such as type 2 diabetes or overweight had a higher risk of developing severe liver fibrosis compared to those without such risk factors, even when given lower cumulative doses of methotrexate [23]. In another study in patients receiving methotrexate, severe liver fibrosis was rare and was not related to the total dose [24]. A US study showed that the combination of obesity, type 2 DM and methotrexate treatment rarely caused terminal liver disease requiring liver transplantation [25].

The effect of methotrexate on the development of fatty infiltration and liver fibrosis is due to the fact that methotrexate polyglutamate inside the cell interferes with the synthesis of pyrimidine and purine, through which it exerts its therapeutic effect [26]. Also methotrexate indirectly affects methylenetetrahydrofolate reductase and promote the formation of methionine from homocysteine. Excess homocysteine causes endoplasmic reticulum stress, which leads to fatty infiltration of the liver [26]. In addition, homocysteine can also activate proinflammatory cytokines and activate hepatic stellate cells, leading to liver fibrosis [26]. Methylenetetrahydrofolate reductase gene polymorphisms (particularly C677T) are associated with methotrexate hepatotoxicity. A meta-analysis demonstrated an Odds Ratio of 4.19 (95% CI 1.6-10.7) for TT versus CC genotype [27].

The risk-benefit assessment of long-term methotrexate therapy depends on the efficacy of the drug in the individual, weighed against the rate of progression of liver fibrosis [3]. The knowledge that long-term methotrexate therapy is associated with the potential for fibrosis that may progress to cirrhosis has led to numerous guidelines recommending intensive monitoring regimens, including liver biopsy at regular intervals. The primary goal of monitoring is to detect liver fibrosis that is clinically significant but reversible upon drug withdrawal. A number of authors recommend serum biomarker algorithms and imaging techniques for clinical practice for non-invasive assessment of the severity of chronic liver disease [28].

In a study evaluating liver fibrosis using transient elastography and noninvasive biochemical methods in patients with rheumatoid arthritis treated with methotrexate for more than 3 years, transient elastography and serological markers of liver fibrosis were assessed [29]. In patients with rheumatoid arthritis treated with high cumulative doses of methotrexate, significant liver fibrosis is rare. The authors recommend transient elastography as an additional diagnostic option for liver fibrosis [29].

Conclusion

DILI is one of the most serious liver diseases; it can be asymptomatic or sudden and lead to death. Timely and dynamic observation of the patient during the administration of any medications at the outpatient and inpatient levels can reduce the risk of developing DILI.

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Conflict of interest

The authors of this article confirmed the absence of a conflict of interest.

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