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Model for predicting risk of developing drug-induced liver injury during remdesivir therapy: observational prospective open case-control study

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Remdesivir is a drug widely used for the etiotropic treatment of COVID-19. According to a number of studies, the incidence of adverse reactions during remdesivir therapy reaches 66%, with the most common is an increase in liver function tests.

The aim of the work was to study the influence of clinical, demographic and pharmacogenetic factors on the development of drug-induced liver damage during remdesivir therapy in COVID-19 patients.

Materials and methods. The study comprised 100 hospitalized patients treated with remdesivir. The patients were divided into two groups: group 1 (n=32) – remdesivir therapy, developed an increase in the level of liver transaminases; group 2 (control, n=68) – did not develop this adverse reaction. The patients in both groups underwent a pharmacogenetic study, and a retrospective analysis of medical records was performed. Based on the data obtained, the association of clinical, laboratory, pharmacological and pharmacogenetic parameters with the development of drug-induced liver damage during remdesivir therapy was studied.

Results. In the group of patients with the development of drug-induced liver damage, people with a high body mass index were significantly more likely than in the control group (30.7±4.2 kg/m^2 in group 1 *vs.* 27.3±5.5 kg/m^2 in group 2, p=0.003), with a history of diabetes mellitus (odds ratio (OR)=2.647, 95% confidence interval (CI)=1.092–6.414, χ^2=4.785, p=0.029), with higher levels of ferritin in the blood (724.03±432.27 and 553.19±358.48 mg/mol, respectively, p=0.040), receiving therapy with angiotensin-converting enzyme inhibitors (OR=5.440, 95% CI=2.160–13.699, χ^2=14.027, p=0.000), statins (OR=3.148, 95% CI=1.307–7.581, χ^2=6.795, p=0.009), and also being heterozygous for the polymorphic marker *rs776746* of the *CYP3A5* gene (OR=3.961, 95% CI=1.343–11.686, χ^2=6.772, p=0.009).

Conclusion. A high body mass index, a history of diabetes mellitus, high levels of ferritin in the blood, concomitant therapy with angiotensin-converting enzyme inhibitors and statins, as well as a carriage of the AG genotype for the polymorphic marker *rs776746* of the *CYP3A5* gene increase the likelihood of developing drug-induced liver damage during remdesivir therapy. In this regard, it is necessary to consider these factors when prescribing remdesivir therapy, conduct a more careful monitoring of clinical and laboratory indicators of liver damage, and develop personalized approaches to the treatment of COVID-19 patients.

Keywords: COVID-19; remdesivir; hepatotoxicity; adverse reactions; predictors of adverse reactions; pharmacogenetic study; clinical trial

Abbreviations: CES1 – carboxyl esterase 1; ALT – alanine aminotransferase; AST – aspartate aminotransferase; ACEI – angiotensin-converting-enzyme; angiotensin-converting-enzyme inhibitors – ACE inhibitors; IL-6 – interleukin-6; BMI – body mass index; DILI – drug-induced liver injury; NSAIDs – non-steroidal anti-inflammatory drugs; ICD – International Classification of Diseases; AR – adverse reaction; PCR – polymerase chain reaction; GFR – glomerular filtration rate.

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Модель прогнозирования риска развития лекарственного поражения печени на фоне терапии ремдесивиром: обсервационное проспективное открытое контролируемое исследование

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Ремдесивир является препаратом, широко используемым для этиотропной терапии COVID-19. Согласно данным ряда исследований, частота развития нежелательных реакций при терапии ремдесивиром достигает 66%, при этом наиболее частой из них является повышение показателей печеночных проб.

Цель. Изучение влияния клинико-демографических и фармакогенетических факторов на развитие лекарственного поражения печени при терапии ремдесивиром у пациентов с COVID-19.

Материалы и методы. В исследование было включено 100 госпитализированных пациентов, получавших лечение препаратом редмесивир. Пациенты были разделены на две группы: группа 1 (*n*=32), у которой на фоне терапии ремдесивиром развилось повышение уровня печеночных трансаминаз; группа 2 (контроль, *n*=68), у которых не было выявлено развития упомянутой нежелательной реакции. Пациентам обеих групп было проведено фармакогенетическое исследование, а также был проведен ретроспективный анализ историй болезни. На основании полученных данных изучена ассоциация клинических, лабораторных, фармакологических и фармакогенетических показателей с развитием лекарственного поражения печени при терапии ремдесивиром.

Результаты. В группе пациентов с развитием лекарственного поражения печени достоверно чаще, чем в группе контроля, встречались лица с высоким индексом массы тела (30,7±4,2 кг/м^2 в группе 1 против 27,3±5,5 кг/м^2 в группе 2, *p*=0,003), имеющие сахарный диабет в анамнезе (отношение шансов (ОШ)=2,647, 95% доверительный интервал (ДИ)=1,092–6,414, χ^2=4,785, *p*=0,029), более высокий уровень ферритина в крови (724,03±432,27 и 553,19±358,48 мг/моль соответственно, *p*=0,040), получавшие терапию ингибиторами ангиотензин-превращающего фермента (ОШ=5,440, 95% ДИ=2,160–13,699, χ^2=14,027, *p*=0,000), статинами (ОШ=3,148, 95% ДИ=1,307–7,581, χ^2=6,795, *p*=0,009), а также являющиеся гетерозиготой по полиморфному маркеру *rs776746* гена *CYP3A5* (ОШ=3,961, 95% ДИ=1,343–11,686, χ^2=6,772, *p*=0,009).

Заключение. Высокий индекс массы тела, сахарный диабет в анамнезе, высокий уровень ферритина в крови, сопутствующая терапия ингибиторами ангиотензин-превращающего фермента и статинами, а также носительство генотипа AG по полиморфному маркеру *rs776746* гена *CYP3A5* повышают вероятность развития лекарственного поражения печени при терапии ремдесивиром. В связи с этим, необходимо учитывать эти факторы при назначении терапии ремдесивиром, проводить более тщательный мониторинг клинических и лабораторных показателей поражения печени и разрабатывать персонализированные подходы к лечению пациентов с COVID-19.

Ключевые слова: COVID-19; ремдесивир; гепатотоксичность; нежелательные реакции; предикторы нежелательных реакций; фармакогенетическое исследование; клиническое исследование

Список сокращений: CES1 – карбоксиэстераза 1; АЛТ – аланинаминотрансфераза; АСТ – аспартатаминотрансфераза; АПФ – ангиотензинпревращающий фермент; иАПФ – ингибиторы АПФ; ИЛ-6 – интерлейкин-6; ИМТ – индекс массы тела; ЛПП – лекарственное поражение печени; НПВП – нестероидные противовоспалительные препараты; НР – нежелательная реакция; МКБ – Международная классификация болезней; ПЦР – полимеразная цепная реакция; СКФ – скорость клубочковой фильтрации.

INTRODUCTION

In the context of the COVID-19 pandemic, there is a need to search for more effective antiviral drugs. Remdesivir is an antiviral drug approved for the treatment of a mild to moderate coronavirus infection. Remdesivir has become widely used in clinical practice, but there are limited data on its safety, pharmacokinetic properties and drug interactions in the treatment of COVID-19.

There are studies on the development of adverse reactions (ARs) during remdesivir therapy. Thus, in a retrospective observational study conducted using the data from the FDA's Adverse Event Reporting System (FAERS), reports of ARs with the use of remdesivir were analyzed for the period from 2019 to 2021. As a result, it was determined that one of the most common ARs was an increase in the liver function tests, the incidence of which was 14.28% [1]. Another retrospective study conducted from September 2020 to February 2021 also found out that the most common AR was elevated liver function tests, with an incidence of 12.9% [2].

The widespread prevalence of drug-induced liver injury (DILI) during remdesivir therapy indicates the need for a further study of its safety, as well as developing methods for a personalized approach patients treatment.

Remdesivir is a prodrug. There is an evidence that 80% of its metabolism occurs under the action of carboxylesterase 1 (*CES1*), which is its main metabolic enzyme, as well as 10% by cathepsin A and 10% by *CYP3A* [3, 4]. In this regard, polymorphism of the genes encoding these enzymes may affect the pharmacokinetics of remdesivir.

Cytochrome P450 of family 3 subfamily A *(CYP3A)* accounts for about 30% of the total content of CYP450 enzymes in the human liver; *CYP3A* enzymes are involved in the metabolism of approximately 50% of drugs [5, 6]. According to the PharmGKB resource [7], some drugs are metabolized with the participation of *CES1*. These two factors indicate that when treating with remdesivir, it is necessary to take into account both the genetic characteristics of patients and concomitant drug therapy.

THE AIM of the work was to study the influence of clinical, demographic and pharmacogenetic factors on the development of drug-induced liver damage during remdesivir therapy in COVID-19 patients.

MATERIALS AND METHODS

Study design

The study was a prospective observational open "case-control" type. The study comprised men and women (*n*=100) aged 18 years and older, hospitalized with a confirmed new coronavirus infection (COVID-19) (U07.1; U07.2 according to the ICD), meeting the inclusion criteria and not meeting the exclusion criteria.

The study was conducted at the city of Moscow Municipal Clinical Hospital No. 15 n.a. O.M. Filatov (Moscow, Russia).

Inclusion criteria for the study were as follows: the established diagnosis of a new coronavirus infection (COVID-19) (U07.1; U07.2 according to the ICD); signed voluntary informed consent to participate in the study; the duration of hospitalization >48 h; the use of remdesivir as etiotropic therapy.

Non-inclusion criteria for the study were as follows: glomerular filtration rate (GFR) less than 30 ml/min/1.73 m^2, pregnancy, breastfeeding, increased alanine aminotransferase (ALT) levels above 5 upper limits of normal ones, a severe liver failure (class C according to Child-Pugh).

Ethical approval

The study complied with the requirements of the World Medical Association's Declaration of Helsinki and was approved by the local ethics committee of the Russian Medical Academy of Continuing Professional Education (RMA CPE) (Protocol No. 15 dated October 16, 2021). A informed consent to participate in this study was obtained from all patients or their legal representatives.

Study duration

The study was conducted between November 2021 and February 2022.

The study comprised 100 hospitalized patients. The age of all patients ranged from 44 to 96 years (the mean age was 73.0±12.5 years). Of these, 31 (31%) were the men, whose average age was 72.91±12.62 years, and 69 (69%) were the women, whose average age was 73.0±12.5 years.

Research methodology

Remdesivir was used in the standard dose: 200 mg IV on the first day, then 100 mg once a day for 5–10 days. The investigator had no influence on the choice of an antiviral drug or a therapy duration.

Subsequently, taking into account the aim of the study, the patients were divided into 2 groups. Group 1 (main group, *n*=32) – patients who, during remdesivir therapy, experienced an increase in transaminase levels, 19 (59%) were the women averagely aged 68.6±12.2 years, as well as 13 (41% of the men) whose average age was 68.5±12.3 years. Group 2 (control group, *n*=68) patients who did not develop DILI during remdesivir therapy, 50 (74%) were the women averagely aged 75.1±12.2 years and 18 (26% of the men) averagely aged 75.0±12.4 years.

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Based on the retrospective analysis of medical histories, it was established that these groups were comparable in gender, anamnesis data – the time of the onset of the disease, the results of the objective examination, the condition severity, concomitant diseases, laboratory parameters, such as a general blood test, a biochemical blood test, including the determination of the total levels of bilirubin, glucose, creatinine, lactate dehydrogenase and indicators of the systemic inflammatory response syndrome: C-reactive protein (CRP), procalcitonin and interleukin-6. The study groups were also comparable in terms of the lung damage degree according to the chest computed tomography data and the duration of hospitalization. At the same time, the groups differed in age, body mass index (BMI), ferritin and D-dimer levels in the blood.

Molecular and genetic research

10 ml of venous blood was collected from the patients using a Vacuette® vacuum system (Greiner Bio-One, Austria) into the tubes with ethylenediaminetetraacetate (EDTA). The whole blood and extracted DNA were stored at –80°C and transported at –20°C. Genotyping was carried out on the basis of the Research Institute of Molecular and Personalized Medicine, the Russian Medical Academy of Continuing Professional Education (Moscow, Russia). The isolation of the genomic DNA from the whole blood was carried out using a set of S-Sorb reagents for the DNA isolation on a silicon sorbent (Syntol LLC, Russia). The concentration of the extracted DNA was determined using a NanoDrop 2000 Spectrophotometer (Thermo Fisher Scientific, USA). The determination of carriage of the single nucleotide polymorphism C>T of the *CYP3A4*22* gene (*rs35599367*) was carried out by allele-specific polymerase chain reaction (PCR) in real time on a CFX96 Touch Real Time System device with a CFX Manager software version 3.0 (BioRad, USA) using the commercial "TaqMan® SNP" kit Genotyping Assays" and "TaqMan Universal Master Mix II" (Applied Biosystems, USA). The carriage of the polymorphic marker A>G of the *CYP3A5*3* gene (*rs776746*) was determined using a commercial reagent kit (Synthol LLC, Russia). The determination of single-nucleotide genetic polymorphisms was carried out by allele-specific PCR in real time on a CFX96 Touch Real Time System device with CFX Manager Software version 3.0 (BioRad, USA). The carriage of the polymorphic marker *rs2244613* (A>C) of the *CES1* gene was detected by a real-time polymerase chain reaction using GenTest *CES1* reagent kits (Nomotek LLC, Russia) on a Real-Time CFX96 Touch amplifier (Bio-Rad Laboratories Inc., USA).

Statistical processing

When statistically processing the results obtained, the standard application package StatSoft Statistica 10.0 (StatSoft, USA) was used. To assess the normality of the quantitative data distribution, graphical (frequency histogram) and calculation methods of Kolmogorov-Smirnov and Shapiro-Wilk were used. Considering the normal distribution of the quantitative data, they were expressed as the arithmetic mean and standard deviation (M±SD); the Student's *t*-test was used to analyze intergroup differences in the quantitative characteristics.

Qualitative indicators are presented as absolute values (*n*) and percentages (%). To identify intergroup differences in the frequencies of qualitative parameters and assess their statistical significance, the χ^2 test (Pearson chi-square) was used. For a small number of observations, Fisher's exact test was calculated. To assess the correlation between the studied parameters, the odds ratio (OR) of the event development with a 95% confidence interval (CI) was calculated. A multivariate regression analysis was also conducted to identify the predictors associated with the development of drug-induced liver injury during remdesivir therapy. The distribution of genotype frequencies of all studied polymorphic markers corresponded to the Hardy-Weinberg equilibrium. The significance of the identified differences and correlations in all types of analysis was accepted at the level of $p < 0.05$.

RESULTS

Gender and age characteristics

The analysis of the demographic data showed that the patients' age of the studied groups was statistically significantly different (p=0.015). In the group of patients with DILI, the average age was 68.6±12.2 years compared to the patients in the control group, whose average age was 75.1±12.2 years. Moreover, the groups were comparable by gender (χ^2=2.038, p=0.153).

Clinical characteristics

When analyzing clinical characteristics, it was revealed that a high BMI was 30.7±4.2 kg/m^2 in the group with DILI *vs.* 27.3±5.5 kg/m^2 in the control group, statistically significantly increases the likelihood of developing DILI during remdesivir therapy (p=0.003). The presence of diabetes mellitus in a patient also increases the likelihood of developing DILI (Table 1).

The analysis of the laboratory data before the start of remdesivir therapy showed that the groups were comparable in terms of general and biochemical blood tests, with a statistically significant difference in ferritin and D-dimer levels. The level of D-dimer was twice higher in the control group (Table 2).

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Table 1 – Comparison of clinical characteristics

Characteristics		Number of patients, *n*		*p*, χ^2	OR (95% CI)
		Main group (group 1) *n*=32	Control group (group 2) *n*=68		
Age, years		68.6±12,2	75.1±12.2	0.015 –	–
Body mass index, kg/m^2		30.7±4,2	27.3±5.5	0.003 –	–
History of adverse reactions		8	15	0.744 0.106	1.178 (0.440–3.152)
Severity of illness	Moderate	22	43	0.793* –	–
	Major	6	13		
	Extreme	4	12		
Comorbidity		28	61	0.742 0.108	0.803 (0.217–2.96)
Cardiovascular diseases		26	59	0.471 0.519	0.661 (0.213–2.049)
Cardiac ischemia		11	30	0.355 0.854	0.663 (0.277–1.588)
Chronic heart failure		4	13	0.411* –	0.663 (0.180–2.026)
Arterial hypertension		28	58	0.767 0.088	1.207 (0.348–4.188)
Diabetes mellitus		15	17	0.029** 4.785	2.647 (1.092–6.414)
Chronic kidney disease		0	14	0.006* –	–
Active cancer (diagnosed earlier than 6 months before study entry)		0	8	0.043* –	–
Encephalopathy		17	44	0.268 1.227	0.618 (0.263–1.452)

Note: OR – odds ratio; CI – confidence interval; *p* – significance level; χ^2 – Pearson's test. **p*-value was comparable to Fisher's exact test. ** Differences are statistically significant.

Table 2 – Laboratory data comparison of main and control groups

Indicators of general and biochemical blood tests	Main group (group 1), *n*=32	Control group (group 2), *n*=68	*p*
Leukocyte count, 10^9/l	6.7±3.8	7.1±3.6	0.652
Absolute neutrophil count, 10^9/l	5.2±3.3	6.9±12.0	0.417
Absolute lymphocyte count, 10^9/l	1.0±0.5	1.1±0.8	0.686
Alanine transaminase, IU/l	33.7±20.4	35.7±38.8	0.791
Aspartic transaminase, IU/l	49.7±22.5	46.1±31.6	0.564
De Ritis coefficient	1.7±0.9	1.8±0.9	0.848
Glucose, mmol/l	7.5±3.8	7.4±3.3	0.851
Creatinine, µmol/l	94.4±16.0	99.3±38.8	0.497
Lactate dehydrogenase, IU/l	432.0±179.3	402.0±180.3	0.438
Ferritin, mg/mol	724.0±432.2	553.1±358.5	0.040**
Interleukin-6, pg/ml	159.3±329.9	100.6±208.1	0.282
Procalcitonin, ng/ml	0.2±0.2	1.6±7.0	0.323
C-reactive protein, mg/l	108.4±75.3	100.5±79.3	0.640
D-dimer, ng/ml	1124.9±1109.0	2225.5±2429.5	0.016**

Note: *p* – significance level. ** Differences are statistically significant.

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Table 3 – Comparison of pathogenetic drug therapy for COVID-19 patients

Drugs	Number of patients, *n*		*p*, χ^2	OR (95% CI)
	Main group (group 1), *n*=32	Control group (group 2), *n*=68		
Glucocorticosteroids	8	15	0.744 0.106	1.178 (0.440–3.152)
Janus kinase inhibitors	30	52	0.036** 4.402	4.615 (0.992–21.467)
Interleukin inhibitors	32	59	0.031** 4.654	–
Repeated administration of interleukin inhibitors	9	15	0.508 0.439	1.383 (0.529–3.613)
Enoxaparin sodium	30	64	0.942 0.005	0.938 (0.163–5.405)

Note: OR – odds ratio; CI—confidence interval; *p*—significance level; χ^2—Pearson's test. ** Differences are statistically significant.

Table 4 – Comparison of drug therapy for concomitant diseases

Drugs	Number of patients, *n*		*p*, χ^2	OR (95% CI)
	Main group (group 1), *n*=32	Control group (group 2), *n*=68		
Antibacterial drugs	14	36	0.391 0.735	0.691 (0.297–1.610)
Antifungal drugs (azoles)	2	2	0.431* –	2,200 (0.296–16.369)
Statins	17	18	0.009** 6.795	3,148 (1.307–7.581)
Beta blockers	9	29	0,163 1,948	0,526 (0.212–1.305)
Calcium channel blockers	7	21	0.349 0.876	0.627 (0.234–1.675)
ACE inhibitors	18	13	0.000** 14.027	5.440 (2.160–13.699)
Angiotensin II receptor blockers (sartans)	2	13	0.093* –	0.282 0.060–1.334
Diuretics	11	23	0.957 0.003	1.025 (0.423–2.485)
Nonsteroidal anti-inflammatory drugs	8	23	0.373 0.792	0.652 (0.254–1.678)
Antipsychotics	4	11	0.631* –	0.740 (0.216–2.534)
Prokinetics	3	12	0.280* –	0.483 (0.126–1.848)
Proton pump inhibitors	31	67	0.581 0.304	0.463 (0.028–7.642)
Biguanides	3	2	0.168* –	3.414 (0.541–21.532)
Salicylates	3	5	0.728* –	1.303 (0.292–5.827)

Note: ACE – angiotensin-converting enzyme; OR – odds ratio; CI – confidence interval; *p* – significance level; χ^2 – Pearson's test. * *p* corresponds to Fisher's exact test. ** Differences are statistically significant.

Table 5 – Genetic data

Gene	Genotype	Number of patients, *n*		*p*, χ^2	OR (95% CI)
		Main group (group 1), *n*=32	Control group (group 2), *n*=68		
CYP3A5 (*rs776746*) A>G	AA	22	61	0.009** 6.772	0.252 (0.086–0.745)
	AG	10	7	0.009** 6.772	3.961 (1.343–11.686)
	GG	0	0	–	–
CYP3A4 (*rs35599367*) C>T	CC	31	65	0.759 0.094	1.431 (0.143–14.317)
	CT	1	3	0.759* –	0.699 (0.070–6.994)
	TT	0	0	–	–
CES1 (*rs2244613*) A>C	AA	25	43	0.136 2.217	2.076 (0.785–5.490)
	AC	4	21	0.048* –	0.320 (0.100–1.027)
	CC	3	4	0.523* –	1.655 (0.348–7.876)

Note: OR – odds ratio; CI – confidence interval; *p* – significance level; χ^2 – Pearson's test. * *p* corresponds to Fisher's exact test. ** Differences are statistically significant.

Table 6 – Risk prediction of drug-induced liver damage during remdesivir therapy

Parameter	Regression coefficient, B±SE	95% CI	OR	*p*
Intercept	–7.195±1.782	[-10.688; -3.702]	–	<0.001
Body mass index	0.183±0.055	[0.075; 0.29]	1.2 [1.08; 1.34]	<0.001
ACE inhibitors	2.215±0.577	[1.083; 3.346]	9.16 [2.95; 28.39]	<0.001
CYP3A5 AG	1.567±0.662	[0.269; 2.864]	4.79 [1.31; 17.54]	0.018

Note: OR – odds ratio; CI – confidence interval; ACE – angiotensin-converting enzyme; *p* – significance level.

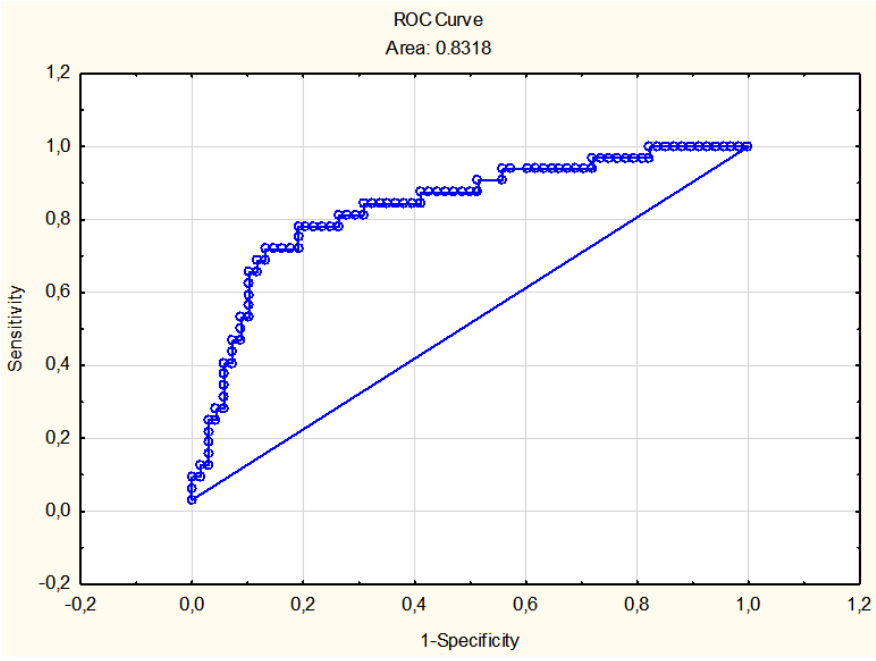

Figure 1 – ROC curve of logistic regression model

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Drug therapy

When analyzing pathogenetic drug therapy for COVID-19, it was revealed that the co-prescription of interleukin inhibitors significantly increases the likelihood of DILI. However, in group 1, the number of patients in whom interleukin inhibitors were used corresponded to 100%, which requires a further study of the effect of pathogenetic drug therapy for COVID-19 on development of DILI during remdesivir therapy in a larger sample. Statistically significant differences in the studied groups for the joint therapy with Janus kinase inhibitors were identified; however, the OR (95% CI) did not reach the level of statistical significance (Table 3).

An analysis of the drug therapy used to treat concomitant diseases showed that the combined use of the drugs from the group of HMG-CoA reductase inhibitors (statins), as well as the group of angiotensin-converting enzyme inhibitors (iACE), significantly increases the chance of developing DILI during remdesivir therapy, the probability increases on average by 3.14 and 5.44 times, respectively (Table 4).

Genetic data

The patients who are heterozygous for the *rs776746* polymorphic marker of the *CYP3A5* gene had a statistically significant likelihood of developing DILI during remdesivir therapy on average 3.96 times higher, while the carriers of the "wild" genotype were significantly less likely to be in the group of patients with DILI (Table 5).

Clinical outcomes

The average duration of hospitalization in group 1 was 12.5±6.9 bed-days, in group 2 – 13.0±10.9 bed-days. There was no statistically significant difference in the duration of hospitalization in the studied groups (p=0.813).

Multivariate logistic regression analysis

As a result of a multivariate logistic regression modeling, an ROC curve was obtained for risk predicting of developing drug-induced liver damage during remdesivir therapy (Fig. 1, Table 6). The modeling was performed with a stepwise elimination based on the Wald Chi-square statistics. The resulting model generalizes 38.9% of the variance in the predicted outcome and allows us to predict the risk of developing DILI in the patients receiving remdesivir, with an accuracy of 83.2%. Moreover, the forecast fully corresponds to the actual data (Hosmer-Lemeshow test, p=0.831).

It was found out that high BMI increases the risk of developing DILI remdesivir therapy by an average of 20% per unit of indicator (p <0.001).

A concomitant use of drugs from the group of ACE inhibitors increases the risk of developing DILI during remdesivir therapy by an average of 9.16 times (p <0.001).

Carriage of the AG genotype for the *rs776746* polymorphic marker of the *CYP3A5* gene increases the risk of developing DILI during remdesivir therapy by an average of 4.79 times compared to other genotypes (p=0.018).

DISCUSSION

According to various studies, the prevalence of ARs during remdesivir therapy ranges from 12[1] to 66% [8]. Moreover, one of the most common ARs is an increase in the activity of ALT and AST, which indicates liver damage. More serious and potentially fatal side effects, including bradycardia and renal failure, have been reported in the literature [9, 10]. Therefore, there is a need to develop a personalized approach for a timely prediction of the complications development when using remdesivir to treat COVID-19 patients. The available scientific works in this area are few.

According to the clinical guidelines, predisposing factors to the development of idiosyncratic DILI as age, gender, pregnancy, malnutrition, obesity and diabetes mellitus, as well as a DILI history[2].

In one of the observational studies, no significant relationship was found between age and the occurrence of ARs during COVID-19 therapy [11]. In the present study, it has been found out that patients who experienced DILI were on average younger in age compared to the group in which patients did not develop this AR. At the same time, no influence of gender on the increased risk of developing DILI has been identified.

In the present study, an association between the development of DILI during remdesivir therapy and an increase in BMI and the presence of diabetes mellitus has been revealed. At the same time, an increase in BMI for each unit of the indicator increases the risk of DILI by an average of 20%.

The course of COVID-19 is associated with actively occurring inflammatory processes [12]. As is known, the factors that cause this inflammation, in particular

[1] U.S. Food and Drug Administration. Gilead Sciences, Inc. VEKLURY® (remdesivir) for injection, for intravenous use. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214787Orig1s010Lbl.pdf

[2] Ministry of Health of the Russian Federation. Clinical recommendations. Drug-induced liver injury (DILI) in adults, 2022. Available from: https://cr.minzdrav.gov.ru/schema/747_1?ysclid=lm9n3chyjg835121911

IL-6, reduce the activity and expression of enzymes of the cytochrome P450 system in the liver [13, 14], which may increase the risk of ARs during COVID-19 pharmacotherapy.

There is an assumption that a key pathogenetic molecular step in the course of COVID-19 is an attack on hemoglobin, leading to the dissociation of porphyrins from iron and the release of iron into the blood circulation. Thus, hemoglobin loses its ability to bind with oxygen and prevents its delivery to the main organs, which is accompanied by a rapid development of multiple organ failure. In addition, the free iron released into the bloodstream can lead to the iron overload, causing oxidative damage to the lungs and other organs. All this dictates an increased absorption and storage of the iron in iron-binding proteins. This is supported by the increased concentration of ferritin in the blood of COVID-19 patients. A high iron load leads to an increased blood viscosity with recurrent and diffuse macro- and microcirculatory thrombosis [15]. Considering this fact, the higher identified ferritin level in the group with DILI may indicate a possible connection between the ferritin level and the risk of developing DILI during remdesivir therapy. A trend towards higher levels of IL-6 in DILI patients has also been identified, but it did not reach a statistically significant difference.

According to the clinical guidelines for DILI in adults, the drugs with a risk of DILI include the following ones: antibacterial drugs, systemic antifungals belonging (azole group), statins, NSAIDs, acetylsalicylic acid, antihypertensive drugs, iACE and calcium channel blockers[3]. No clinical drug interaction studies have been fixed with remdesivir[4].

According to the clinical studies, the most common adverse event with the use of interleukin inhibitors was the liver damage, manifested by an increase in the activity of hepatic transaminases (ALT, AST), with an incidence of 3.7 to 35.8% [16–23]. The STOP-COVID study [24] showed that the highest incidence of liver enzyme elevations was observed in Janus kinase inhibitor therapy (4.2%).

In this regard, when remdesivir is co-administered with these drugs, the risk of liver toxicity theoretically increases. It has been found out that the concomitant therapy with iACE, statins and interleukin inhibitors increase the risk of developing DILI. In treatment with iACE, this risk increases by an average of 9.16 times. Statistically significant differences in the studied groups for joint therapy with Janus kinase inhibitors with an increase in the likelihood of DILI during joint therapy with this group of drugs have also been identified, but the OR (95% CI) did not reach the statistical significance level.

Remdesivir is extensively metabolized to GS-443902, a pharmacologically active nucleoside triphosphate analogue. Remdesivir is initially hydrolyzed by esterases to form the intermediate metabolite GS-704277. Carboxylesterase 1 and cathepsin A are responsible for 80 and 10% of the remdesivir metabolism, respectively, and *CYP3A* is responsible for the remaining 10%. Phosphoramidate cleavage of GS-704277 and a further phosphorylation of the resulting monophosphate nucleoside analogue leads to the formation of GS-443902. Dephosphorylation of all phosphorylated metabolites can lead to the formation of the nucleoside analogue GS-441524 [25].

*CYP3A5*3,* defined by an intronic variant (NM_000777.5: c.219-237A>G; *rs776746*), is associated with poor metabolism (historically also known as a non-expressor phenotype) [5]. As a result of the study, it was revealed that carriage of the AG genotype for the polymorphic marker *rs776746* of the *CYP3A5* gene is associated with an increase in the risk of developing drug-induced liver damage during remdesivir therapy by an average of 4.79 times relative to other genotypes.

Study limitations

The limitations of the present study were as follows: a small sample size, so some possible clinically significant associations between the factors could not be proven by statistical methods; a limited number of candidate genes and allelic variants in the analysis, and a limited follow-up period. The study was a “case-control” design and has inherent limitations.

CONCLUSION

The analysis results of the relationship between the development of DILI during remdesivir therapy with gender and age, clinical, anamnestic and laboratory parameters and concomitant drug therapy showed that a high BMI, a history of diabetes mellitus, a high level of ferritin in the blood, joint therapy with iACE and statins, and also carriage of the AG genotype for the *rs776746* polymorphic marker of the *CYP3A5* gene, was significantly more common in patients with DILI. The results obtained indicate that when prescribing remdesivir therapy, it is necessary to take these factors into account with more careful monitoring of clinical and laboratory signs of liver damage in these groups of patients, and in the future, to develop a personalized approach to pharmacotherapy of COVID-19 patients.

[3] Ibid.
[4] U.S. Food and Drug Administration. Gilead Sciences, Inc. VEKLURY® (remdesivir) for injection, for intravenous use, 2022

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Yulia V. Shevchuk – idea and concept of the study, conducting the study, systematizing literature data, writing and editing the text of the manuscript, formulating conclusions; Alexander V. Kryukov – idea and development of the manuscript concept, systematization of literary data, text editing, formulation of conclusions, approval of the final version of the manuscript for publication; Ilyas I. Temirbulatov – analysis and interpretation of the literature data, participation in the research, analysis and discussion of the results obtained; Ivan V. Sychev – statistical data processing, editing the manuscript text, formulation of conclusions; Karin B. Mirzaev – development of the research concept, critical revision of the content and results of the work, editing the text of the manuscript; Natalya P. Denisenko – analysis and interpretation of the literature data, editing the manuscript, participation in the study; Sherzod P. Abdullaev – analysis of the literature data, editing of the manuscript text; Svetlana N. Tuchkova – laboratory processing of materials; Valery I. Vechorko – critical revision of the manuscript, approval of the final version of the manuscript sections; Oleg V. Averkov – participation in the development of the manuscript concept, editing the manuscript sections; Dmitry A. Sychev – development of the research concept, critical analysis of the results obtained, approval of the final version of the manuscript for publication. All the authors confirm that their authorship meets the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved the final version before the publication).

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