DOI: 10.20514/2226-6704-2020-10-3-165-187

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Drug Safety Issues in Therapy COVID-19

Abstract

One of the serious problems of modern Health care is a new coronavirus infection — COVID-19, which has been declared a global pandemic by the World Health Organization and has covered more than 190 countries. Despite the measures has been taken to limit contacts between people and isolate patients with suspected coronavirus infection, the number of cases grows exponentially every day. Leading laboratories are working on a vaccine, but according to some optimistic forecasts, it may be available no earlier than 11-12 months. According to published data on attempts using various drug regimens in clinical trials, methodological manuals and clinical guidelines for patient management are constantly being developed and updated depending on the severity of the condition. The appointment of a number of drug combinations should be carried out taking into account the definition of an individual assessment of the benefits and risks, because there is ample evidence of serious side effects.

More serious lung tissue lesions are characteristic of patients of an older age group (over 60 years old) with the presence of concomitant diseases, such as cardiovascular, cerebrovascular, diabetes mellitus and obesity, diseases of the bronchopulmonary system and kidneys, which implies taking basic therapy in a constant mode. The appointment of a number of drug combinations should be carried out taking into account the definition of an individual assessment of the benefits and risks, because there is enough evidence of serious side effects, such as the QT interval prolongation, hepatotoxicity, adverse events from the central nervous system. It is necessary to evaluate the interaction of drugs used to treat infections caused by the COVID-19 virus with drugs used in outpatient practice.

Key words: *COVID-19, treatment, safety, drug interaction, contraindications*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 17.04.2020

Accepted for publication on 20.05.2020

For citation: Levitova D.G., Gracheva S.A., Samoylov A.S. et al. Drug Safety Issues in Therapy COVID-19. The Russian Archives of Internal Medicine. 2020; 10(3): 165-187. DOI: 10.20514/2226-6704-2020-10-3-165-187

ACEI — angiotensin converting enzyme inhibitors, AKI — acute kidney injury, ALT — alanine aminotransferase, ARBs — angiotensin II receptor blockers, BMI — body mass index, CTs — clinical trials, GCSs — glucocorticosteroids, CKD — chronic kidney disease, COVID-19 — coronavirus disease 2019, ECG — electrocardiogram, GIT — gastrointestinal tract, HIT — heparin-induced thrombocytopenia, HIV — human immunodeficiency virus, IL-6 — interleukin-6, LMWH — low-molecular-weight heparin, NSAIDs — nonsteroidal anti-inflammatory drugs, RNA — ribonucleic acid, TdP — torsade de pointes, UNL — upper normal limit

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The most pressing challenge facing medicine in the world today is combating coronavirus disease (COVID-19). This disease is caused by the novel coronavirus strain — SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).

The biggest challenge in managing COVID-19 patients is the lack of drugs with proven efficacy and established treatment regimens based on clinical trials (CTs). Everywhere, there are ongoing attempts to use drugs with expected effectiveness. CTs are being conducted. Data on the first CT results and experience of using different drugs are being analyzed on the fly; clinical guidelines are being developed and continuously updated.

The following drugs are the most frequently used for managing COVID-19 patients, taking into account, among other things, the experience of previous outbreaks of coronavirus infections (severe acute respiratory syndrome, Middle East respiratory syndrome): aminoquinoline derivatives (chloroquine, hydroxychloroquine) [1], antiviral drugs, in particular, with effects against human immunodeficiency virus (lopinavir/ritonavir [2], darunavir [3]), anti-influenza antiviral drugs (oseltamivir [4], favipiravir [5]), other antiviral drugs (ribavirin [6], remdesivir [7]), macrolide antibiotics [8] (azithromycin), interferons (recombinant interferon beta-1b [9] and others), and monoclonal antibodies [10]. There are data on the use of other drugs: nafamostat [11], camostat [12], niclosamide [13], baricitinib [14], danoprevir [15], nitazoxanide [16], and teicoplanin [17].

There is extensive debate over the use of remdesivir as an antiviral drug for treating SARS-CoV-2 infection. This drug provides the most effective and highly selective inhibition of viral RNA synthesis in low micromolar concentrations. However, this drug is still at the clinical trial stage and is not available for real-life clinical use [18].

The following medications are recommended in the Russian Federation: mefloquine, chloroquine, hydroxychloroquine, lopinavir/ritonavir, darunavir, azithromycin, recombinant interferon beta-1b, tocilizumab, sarilumab, baricitinib [19–21]. At the moment, all of the above drugs are "off-label". They can be prescribed only by a medical board provided that their potential benefit outweighs possible risks for the patient. It should be remembered that all drugs have side effects that can develop or intensify when used together or in combinations that were previously not widely used, for example, in intensive care. This particularly applies to elderly patients who are at higher risk of contracting coronavirus disease.

We analyzed possible side effects mentioned in literature, as well as interactions between drugs used to treat COVID-19 and possible concomitant treatment; this can help in choosing a personalized and safest treatment regimen for each patient, taking into account concomitant pathologies and treatment. Results of the analysis of interactions are presented in Tables 1–4. Most side effects of drugs used against COVID-19 appear during their long-term use for main indications. The clinical significance of their short-term use is hard to assess at the moment. However, these side effects should be considered when choosing treatment regimens (Table 1).

COVID-19 Treatment and Risk of Heart Rhythm Disorders

One of the serious side effects that are typical of some groups of drugs (Table 2) used in COVID-19 patients is QT prolongation and the risk of torsade de pointes (TdP), which requires attention and mandatory monitoring of electrocardiography (ECG) results.

Risk factors for TdP caused by drug toxicity include: elderly age, the female sex, acute myocardial infarction, heart failure with reduced ejection fraction, hypokalemia, hypomagnesemia, hypocalcemia, bradycardia, loop diuretics, sepsis, and genetic predispositions [22]. The QT prolongation risk assessment scale can help to assess risks (Table 3) [23, 24].

One of the most frequently prescribed anti-COVID-19 treatment regimens that stands out is the combination of hydroxychloroquine and azithromycin, as well as other possible combinations of aminoquinoline derivatives and macrolides, since both groups of drugs can prolong the QT interval. Besides the QT interval, lopinavir/ritonavir can prolong the PQ interval. Moreover, patients may already take drugs that prolong QT, for example, amiodarone, alfuzosin, amitriptyline, fluoroquinolones and others. When choosing

Table 1. *Features of the use of drugs against COVID-19 in patients with risk factors **

	Dose adjustment for renal failure	Dose adjustment for liver failure	The risk of lengthening the QT interval
Mefloquine	Not required	No data — use with caution	Yes
Chloroquine	50% dose reduction, with CC <10 ml/min	No data — use with caution	Yes
Hydroxychloroquine	No data — use with caution	No data — use with caution	Yes
Lopinavir/ritonavir	No data — use with caution	No data — use with caution	Yes
Darunavir	Not required	Not required, for severe violations of liver function no data — use with caution	No
Ribavirin	With CC <50 ml/min is contraindicated	Contraindicated in severe liver failure	No
Interferon-β 1b	Not required, with severe renal failure — with caution	Not required, use under control of hepatic transaminase levels	No
Tocilizumab	Not required for mild renal impairment; patients with moderate to severe renal impairment no data — use with caution	No data — use with caution	No
Baricitinib	Required for CC <60 ml / min, with CC <30 ml/min is contraindicated	Not required, for severe violations of liver function use with caution	No
Sarilumab	No data — use with caution	No data — use with caution	No

Note: CC — creatinine clearance
* Risk factors: a medical history of heart rhythm disturbance, a presence of renal and / or liver failure, taking nephro-, hepato-, cardiotoxic drugs

a treatment regimen, especially if no ECG or laboratory control can be performed, for example, when providing medical care at home or at a distance, possible risks of life-threatening arrhythmias should be carefully assessed before choosing the treatment regimen.

Aminoquinoline Derivatives

Neurological and psychiatric side effects of aminoquinoline derivatives require the special attention of medical staff; they can appear as headaches, anxiety, confusion, insomnia, dizziness, personality disorders, memory impairment, hallucinations, speech impairment, visual impairment, depression, suicidal thoughts, hearing loss, psychoses, convulsions, polyneuropathy, and paresthesias. There are various mechanisms of neurotoxicity [25]. It should be noted that the half-life of drugs is quite long (from 2 to 8 weeks); hence, side effects can appear after drug withdrawal. Attention should also be paid to the risk of interaction of aminoquinoline derivatives and drugs used in neurology and psychiatry (Tables 4).

Eye lesions when using aminoquinoline derivatives are a serious side effect as they can lead to irreversible loss of vision, especially in elderly patients and in patients with known retinal lesions. This phenomenon arises from the binding of the drugs to retinal melanin, which leads to the dystrophy of the pigmented layer. Symptoms of retinopathy can appear in the form of diminished clarity and partial loss of central or peripheral vision, flashing and halos, impaired color perception, difficulty in reading, gross pigmentation changes with so-called "bull's eye" effect. However, the initial stages are asymptomatic [26]. Symptoms usually appear when treatment lasts for more than five years [27]. However, there are clinical observations that show the appearance of typical retinal injuries two months after the beginning of hydroxychloroquine therapy. This can be explained by a genetic predisposition [28, 29] or by excessive concentration in the blood caused by doses higher than recommended ones, impaired renal or hepatic function, co-administration with drugs that affect hydroxychloroquine metabolism at the level of cytochrome P450 (CYP2D6) [30, 31].

Table 2. *The interaction of drugs among themselves, used to treat infections caused by the COVID-19 virus, with drugs used in the hospital*

	Мефлохин / Mefloquine	**Хлорохин / chloroquine**	**Гидроксихлорохин / hydroxychloroquine**	**Лопинавир/ нитонавир/ lopinavir/ ritonavir**	**Дарунавир/ darunavir**	**Сарилумаб/ sarilumab**
Теофиллин / Theophylline				Увеличивается концентрация теофиллина / Theophylline concentration increases	Увеличивается концентрация теофиллина / Theophylline concentration increases	Увеличивается метаболизма теофиллина / Theophylline metabolism increases
Салметерол / Salmeterol	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация сальметерола / Salmeterol concentration increases	Увеличивается концентрация сальметерола / Salmeterol concentration increases	
Будесонид / Budesonide				Увеличивается концентрация будесонида, снижается концентрация лопинавира, ритонавира / Budesonide concentration increases, lopinavir and ritonavir concentration decreases	Увеличивается концентрация будесонида, снижается концентрация дарунавира / Budesonide concentration increases, concentration darunavir decreases	
Дексаметазон / Dexamethasone	Риск развития миопатии, в т.ч. кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Риск развития миопатии, в т.ч. кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Риск развития миопатии, в т.ч. кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Увеличивается концентрация дексаметазона, снижается концентрация лопинавира, ритонавира / Dexamethasone concentration increases, lopinavir and ritonavir concentration decreases	Увеличивается концентрация дексаметазона, снижается концентрация дарунавира / Dexamethasone concentration increases, darunavir concentration decreases	
Метилпреднизолон / Methylprednisolone	Риск развития миопатии, в т.ч. Кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Риск развития миопатии, в т.ч. Кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Риск развития миопатии, в т.ч. Кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Увеличивается концентрация метилпреднизолона, снижается концентрация лопинавира, ритонавира / Methylprednisolone concentration increases, lopinavir and ritonavir concentration decreases	Увеличивается концентрация метилпреднизолона, снижается концентрация дарунавира / Methylprednisolone concentration increases, darunavir concentration decreases	
Флутиказон / Fluticasone				Увеличивается концентрация флутиказона / Fluticasone concentration increases	Увеличивается концентрация флутиказона / Fluticasone concentration increases	
Беклометазон / Beclometasone				Возможно развитие системных побочных эффектов беклометазона / Perhaps the development of systemic side effects of beclomethasone		

	Мефлохин / Mefloquine	**Хлорохин / chloroquine**	**Гидроксихлорохин / hydroxychloroquine**	**Лопинавир/ hитонавир/ lopinavir/ ritonavir**	**Дарунавир/ darunavir**	**Сарилумаб/ sarilumab**
Парацетамол / Paracetamol	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia			
Морфин / Morphine		Увеличивается концентрация морфина / Morphine concentration increases		Увеличивается концентрация морфина / Morphine concentration increases		
Фентанил / Fentanyl	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia	Увеличивается концентрация фентанила / Fentanyl concentration increases	Увеличивается концентрация фентанила / Fentanyl concentration increases	
Диазепам / Diazepam				Увеличивается концентрация диазепама / Diazepam concentration increases	Увеличивается концентрация диазепама / Diazepam concentration increases	
Галоперидол / Haloperidol	Увеличивается концентрация мефлохина, риск удлинения QT / Mefloquine concentration increases, risk of QT prolongation	Увеличивается концентрация галоперидола / Haloperidol concentration increases	Риск удлинения QT / QT prolongation risk	Увеличивается концентрация галоперидола, риск удлинения QT / Haloperidol concentration increases, risk of QT prolongation		
Кветиапин / Quetiapine	Риск удлинения QT/ QT prolongation risk	Риск удлинения QT/ QT prolongation risk	Риск удлинения QT / QT prolongation risk	Увеличивается концентрация кветиапина / Quetiapine concentration increases	Увеличивается концентрация кветиапина / Quetiapine concentration increases	
Дроперидол / Droperidol			Риск удлинения QT, ЭКГ-контроль / QT prolongation risk, ECG monitoring			
Клоназепам / Clonazepam				Увеличивается концентрация клоназепама / Clonazepam concentration increases	Увеличивается концентрация клоназепама / Clonazepam concentration increases	
Рисперидон / Risperidone	Риск удлинения QT / QT prolongation risk	Увеличивается концентрация рисперидона / Risperidone concentration increases	Риск удлинения QT/ QT prolongation risk	Увеличивается концентрация рисперидона / Risperidone concentration increases		

	Мефлохин / Mefloquine	Хлорохин / chloroquine	Гидроксихлорохин / hydroxychloroquine	Лопинавир/ ҺИТОНАВИР/ lopinavir/ ritonavir	Дарунавир/ darunavir	Сарилумаб/ sarilumab
Вальпроевая кислота / Valproic acid	Уменьшается концентрация вальпроевой кислоты / Valproic acid concentration decreases			Снижается концентрация вальпроевой кислоты, контроль концентрации / Valproic acid concentration decreases, concentration control		
Севофлуран / Sevoflurane	Риск удлинения QT/ QT interval prolongation			Риск удлинения QT/ QT interval prolongation		
Изофлюран / Isoflurane	Риск удлинения QT/ QT interval prolongation			Риск удлинения QT/ QT interval prolongation		
Дабигатран / Dabigatran etexilate	Увеличивается концентрация дабигатрана / Dabigatran concentration increases			Увеличивается концентрация дабигатрана, риск кровотечений / Dabigatran concentration increases, the risk of bleeding	Увеличивается концентрация дабигатрана, риск кровотечений / Dabigatran concentration increases, the risk of bleeding	
Ривароксабан / Rivaroxaban	Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding			Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding	Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding	
Апиксабан / Apixaban				Увеличивается концентрация апиксабана, риск кровотечений / Apixaban concentration increases, risk of bleeding	Увеличивается концентрация апиксабана, риск кровотечений / Apixaban concentration increases, risk of bleeding	
Тикагрелор / Ticagrelor	Увеличивается концентрация мефлохина / Mefloquine concentration increases			Увеличивается концентрация тикагрелора / Ticagrelor concentration increases	Увеличивается концентрация тикагрелора / Ticagrelor concentration increases	
Клопидогрель / Clopidogrel				Ритонавир уменьшает концентрацию клопидогреля / Ritonavir reduces clopidogrel concentration	Уменьшается концентрация клопидогреля / Clopidogrel concentration decreases	
Октреотид / Octreotide	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	
Ондансетрон / Ondansetron	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация ондасетрона. Риск удлинения QT / Ondsetron concentration increases. QT interval prolongation	

	Мефлохин / Mefloquine	Хлорохин / chloroquine	Гидроксихлорохин / hydroxychloroquine	Лопинавир/ hитонавир/ lopinavir/ ritonavir	Дарунавир/ darunavir	Сарилумаб/ sarilumab
Дигоксин / Digoxin			Увеличивается концентрация дигоксина / Digoxin concentration increases	Ритонавир увеличивает концентрацию дигоксина, контроль концентрации дигоксина / Ritonavir increases digoxin concentration, control digoxin concentration		
Амиодарон / Amiodarone	Увеличивается концентрация мефлохина, риск удлинения QT / Mefloquine concentration increases, risk of QT prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация амиодарона, риск аритмий / Amiodarone concentration increases, the risk of arrhythmias	Увеличивается концентрация амиодарона / Amiodarone concentration increases	
Верапамил / Verapamil	Увеличивается концентрация верапамила, мефлохина, риск аритмии / Verapamil, mefloquine increases, the risk of arrhythmia			Увеличивается концентрация верапамила, лопинавира, ритонавира / Verapamil, lopinavir, ritonavir increases	Увеличивается концентрация верапамила / Verapamil concentration increases	
Эсмолол / Esmolol	Увеличивается концентрация эсмолола, риск аритмии / Esmolol concentration increases, the risk of arrhythmia					
Спиронолактон / Spironolactone				Увеличивается концентрация ритонавира / Ritonavir concentration increases		
Ампициллин / Ampicillin		Снижается концентрация ампициллина при приеме внутрь / Oral ampicillin concentration decreases				
Амикацин / Amikacin				Увеличивается концентрация амикацина / Amikacin concentration increases		
Моксифлоксацин / Moxifloxacin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	

	Мефлохин / Mefloquine	Хлорохин / chloroquine	Гидроксихлорохин / hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ ritonavir	Дарунавир/ darunavir	Сарилумаб/ sarilumab
Левофлоксацин / Levofloxacin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	
Ципрофлоксацин / Ciprofloxacin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	
Азитромицин / Azithromycin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация ритонавира, увеличивается токсичность лопинавира, риск удлинения QT / Ritonavir concentration increases, the toxicity of lopinavir increases, the risk of QT prolongation	Риск удлинения QT/ QT interval prolongation	
Кларитромицин / Clarithromycin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация лопинавира/ритонавира, кларитромицина, риск удлинения QT / Lopinavir/ritonavir and clarithromycin concentration increases, the risk of QT prolongation		
Эритромицин / Erythromycin	Увеличивается концентрация мефлохина / Mefloquine concentration increases	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация эритромицина, лопинавира, ритонавира. Риск удлинения QT / Erythromycin, lopinavir and ritonavir concentration increases. QT prolongation risk	Увеличивается концентрация эритромицина, дарунавира / Erythromycin and darunavir concentration increases	
Флуконазол / Fluconazole	Увеличивается концентрация мефлохина / Mefloquine concentration increases		Риск удлинения QT/ QT interval prolongation		Увеличивается концентрация дарунавира / Darunavir concentration increases	
Инсулин / Insulin				Снижается эффект инсулина, риск гипергликемии / The effect of insulin is reduced, the risk of hyperglycemia	Снижается эффект инсулина, риск гипергликемии / The effect of insulin is reduced, the risk of hyperglycemia	
Левотироксин/ Levothyroxine				Ритонавир снижает эффективность левотироксина, коррекция дозы / Ritonavir reduces the effectiveness of levothyroxine, dose adjustment		

Another rare but typical aminoquinoline side effect is methemoglobinemia, and as a result, impaired oxygen delivery to tissues, which can lead to deterioration in patients with viral pneumonia. Risk factors for this serious complication include: age below 3 months, elderly age, congenital enzymopathies (cytochrome b5 reductase deficiency), congenital hemoglobinopathies, combination of drugs that can trigger methemoglobinemia (benzocaine, prilocaine, paracetamol, fentanyl, etc.), severe concomitant pathologies (cardiovascular, renal, respiratory failure, hematological diseases) [32].

There are clinical observations that describe the risk of hypoglycemia when taking chloroquine and hydroxychloroquine. This can be explained not only by the manifestation of an underlying disease (malaria) but also other factors (decreased insulin clearance, increased sensitivity of peripheral tissues to insulin and stimulation of insulin secretion by pancreatic beta cells) [33, 34].

Table 3. Risk assessment of QT interval prolongation

Risk factor	Points
Age ≥68 years	1
Female	1
Receiving loop diuretics	1
Blood potassium level ≤3.5 mmol / L	2
Original QTc ≥450 ms	2
Acute myocardial infarction	2
Heart failure	3
Sepsis	3
Taking one QT extension drug	3
Co-administration of 2 or more drugs that prolong QT *	3
Maximum points	21
Risk assessment:	
Low risk (15%)	<7
Medium risk (37%)	7-10
High risk (73%)	≥11

Note: * — when taking 2 or more drugs, it is worth summing up the points for taking one drug and the combined intake of 2 or more drugs that extend QT

Azithromycin

A rare but serious side effect of azithromycin is drug-induced liver injury that is characterized by a sharp increase of alanine aminotransferase (ALT) with short courses of treatment (3–4 days) [35, 36].

Although it is generally accepted that azithromycin has the lowest cardiotoxicity among macrolides [37], there is still a small risk of sudden death related to a five-day course in patients at high cardiovascular risk [38].

Lopinavir/Ritonavir

It was reported that the administration of lopinavir/ritonavir can be an independent risk factor for kidney damage that can present as acute kidney injury (AKI), chronic kidney disease, acute and chronic interstitial nephritis, nephrolithiasis, asymptomatic crystalluria, papillary necrosis in HIV-positive patients, with long-term use, both with the history of impaired renal function, and with a normal baseline function [39–42]. A case of AKI was reported in a patient without confirmed HIV infection who took lopinavir/ritonavir for post-exposure prophylaxis for less than seven days, with regression of symptoms after drug withdrawal [43]. One of the causes of AKI related to lopinavir/ritonavir may be interaction with drugs of other groups at the level of cytochrome P450 since ritonavir is a CYP3A4 inhibitor. Their interaction with statins raises blood concentration and the risk of rhabdomyolysis and AKI [44]. Interaction with nifedipine also increases its blood concentration. There was a report on the development of severe hypotension and AKI related to its combined use with lopinavir/ritonavir [45].

A small study including HIV-negative healthy volunteers demonstrated that five days after taking lopinavir/ritonavir, levels of triglycerides and free fatty acids increase, and signs of insulin resistance appear [46].

Tocilizumab and Sarilumab

The development of infections is a serious side effect of using tocilizumab and sarilumab; it is caused by the primary pharmacological effect of these drugs, i.e., inhibition of interleukin-6 (IL-6) that is involved in the immune response to bacterial, viral and fungal pathogens [47–50].

Table 4. *The interaction of drugs against COVID-19 with drugs used in outpatient practice*

	Мефлохин/ mefloquine	**Хлорохин/ chloroquine**	**Гидроксихлорохин / Hydroxychloroquine**	**Лопинавир/ ритонавир/ lopinavir/ritonavir**	**Дарунавир/ darunavir**	**Рибавирин/ ribavirin**	**Барицитиниб/ baricitinib**	**Сарилумаб/ sarilumab**
Валсартан / Valsartan				Ритонавир увеличивает концентрацию валсартана / Ritonavir increases valsartan concentration				
Амлодипин / Amlodipine	Увеличивается концентрация амлодипина, риск аритмий / Amlodipine concentration increases, the risk of arrhythmia				Увеличивается концентрация амлодипина / Amlodipine concentration increases			
Фелодипин / Felodipine	Увеличивается концентрация фелодипина, риск аритмий / Felodipine concentration increases, the risk of arrhythmia			Увеличивается концентрация фелодипина / Felodipine concentration increases	Увеличивается концентрация фелодипина / Felodipine concentration increases			
Нифедипин / Nifedipine	Увеличивается концентрация нифедипина, риск аритмий / Nifedipine concentration increases, the risk of arrhythmia			Увеличивается концентрация нифедипина / Nifedipine concentration increases	Увеличивается концентрация нифедипина и дарунавира / Nifedipine and darunavir concentration increases			
Индапамид / Indapamide	Увеличивается токсичность индапамида, риск удлинения QT / Indapamide toxicity is increased, QT prolongation risk							
Бисопролол / Bisoprolol	Увеличивается концентрация бисопролола, риск аритмий / Bisoprolol concentration increases, the risk of arrhythmia							
Метопролола тратрат, метопролола сукцинат/ Metoprolol tartrate, metoprol succinate	Увеличивается концентрация метопролола, риск аритмий / Metoprolol concentration increases, the risk of arrhythmia	Увеличивается концентрация метопролола / Metoprolol concentration increases		Ритонавир увеличивает концентрацию метопролола / Ritonavir increases metoprolol concentration	Увеличивается концентрация метопролола / Metoprolol concentration increases			

	Мефлохин/ mefloquine	Хлорохин/ chloroquine	Гидроксихлорохин / Hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ritonavir	Дарунавир/ darunavir	Рибавирин/ ribavirin	Барицитиниб/ baricitinib	Сарилумаб/ sarilumab
Небивалол / Nebivolol	Увеличивается концентрация небилола, риск аритмий / Nebivalol concentration increases, the risk of arrhythmia	Увеличивается концентрация небивалола / Nebivalol concentration increases		Ритонавир увеличивает концентрацию небивалола / Ritonavir increases nebivalol concentration				
Силденафил при лечении легочной артериальной гипертензии / Sildenafil in the treatment of pulmonary arterial hypertension				Возможно значительное повышение концентрации силденафила, риск гипотензии, приапизма / Perhaps a significant increase in the concentration of sildenafil, the risk of hypotension, priapism	Увеличивается концентрация силденафила, риск гипотензии, синкопе,приапизма / Sildenafil concentration increases, the risk of hypotension, syncope, priapism			
Силденафил для лечения эректильной дисфункции / Sildenafil for the treatment of erectile dysfunction				Возможно значительное повышение концентрации силденафила, риск гипотензии, приапизма / Perhaps a significant increase in the concentration of sildenafil, the risk of hypotension, priapism	Увеличивается концентрация силденафила, риск гипотензии, синкопе,приапизма / Sildenafil concentration increases, the risk of hypotension, syncope, priapism			
Алфузозин / Alfuzosin	Риск удлинения QT/ QT interval prolongation		Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация алфузозина, риск тяжелой артериальной гипертензии / Alfuzosin concentration increases, the risk of severe arterial hypertension	Увеличивается концентрация алфузозина / Alfuzosin concentration increases			
Амиодарон / Amiodarone	Увеличивается концентрация мефлохина, риск удлинения QT / Mefloquine concentration increases, risk of QT prolongation		Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация амиодарона, риск аритмий / Amiodarone concentration increases, the risk of arrhythmias	Увеличивается концентрация амиодарона / Amiodarone concentration increases			

	Мефлохин/ mefloquine	Хлорохин/ chloroquine	Гидроксихлорохин / Hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ritonavir	Дарунавир/ darunavir	Рибавирин/ ribavirin	Барицитиниб/ baricitinib	Сарилумаб/ sarilumab
Дигоксин / Digoxin			Увеличивается концентрация дигоксина / Digoxin concentration increases	Ритонавир увеличивает концентрацию дигоксина, контроль концентрации дигоксина / Ritonavir increases digoxin concentration, control digoxin concentration				
Аторвастатин / Atorvastatin				Увеличивается концентрация аторвастатина, применение минимальных доз, риск рабдомиолиза / Atorvastatin concentration increases, the use of minimal doses, the risk of rhabdomyolysis	Увеличивается концентрация аторвастатина, применение минимальных доз, риск рабдомиолиза / Atorvastatin concentration increases, the use of minimal doses, the risk of rhabdomyolysis			Снижение активности аторвастатина/ reduced activity of atorvastatin
Розувастатин / Rosuvastatin				Увеличивается концентрация розувастатина, применение минимальных доз, риск рабдомиолиза / Rosuvastatin concentration increases, the use of minimal doses, the risk of rhabdomyolysis	Увеличивается концентрация розувастатина, применение минимальных доз, риск рабдомиолиза / Rosuvastatin concentration increases, the use of minimal doses, the risk of rhabdomyolysis			
Симвастатин / Simvastatin				Увеличивается концентрация симвастатина, риск рабдомиолиза / Simvastatin concentration increases, the risk of rhabdomyolysis	Увеличивается концентрация симвастатина, риск рабдомиолиза / Simvastatin concentration increases, the risk of rhabdomyolysis			Снижение активности симвастатина/ reduced activity of simvastatin
Клопидогрель / Clopidogrel				Ритонавир уменьшает концентрацию клопидогреля / Ritonavir reduces clopidogrel concentration	Уменьшается концентрация клопидогреля / Clopidogrel concentration decreases			
Тикагрелор / Ticagrelor	Увеличивается концентрация мефлохина / Mefloquine concentration increases			Увеличивается концентрация тикагрелора / Ticagrelor concentration increases	Увеличивается концентрация тикагрелора / Ticagrelor concentration increases			

	Мефлохин/ mefloquine	Хлорохин/ chloroquine	Гидроксихлорохин / Hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ritonavir	Дарунавир/ darunavir	Рибавирин/ ribavirin	Барицитиниб/ baricitinib	Сарилумаб/ sarilumab
Варфарин / Warfarin				Возможно увеличение концентрации варфарина / Warfarin concentration possible increased	Уменьшается концентрация варфарина / Warfarin concentration decreases	Уменьшается концентрация варфарина / Warfarin concentration decreases		Возможно увеличение концентрации варфарина / Warfarin concentration possible increased
Дабигатран / Dabigatran etexilate	Увеличивается концентрация дабигатрана / Dabigatran concentration increases			Увеличивается концентрация дабигатрана, риск кровотечений / Dabigatran concentration increases, the risk of bleeding	Увеличивается концентрация дабигатрана, риск кровотечений / Dabigatran concentration increases, the risk of bleeding			
Ривароксабан / Rivaroxaban	Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding			Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding	Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding			
Апиксабан / Apixaban				Увеличивается концентрация апиксабана, риск кровотечений / Apixaban concentration increases, risk of bleeding	Увеличивается концентрация апиксабана, риск кровотечений / Apixaban concentration increases, risk of bleeding			
Рабепразол / Rabeprazole				Ритонавир снижает уровень рабепразола / Ritonavir reduces Rabeprazole level	Увеличивается концентрация рабепразола / Rabeprazole concentration Increased			
Глимепирид / Glimepiride				Ритонавир может увеличивать или умешать концентрацию глимепирида, лопинавир снижает эффект глимеперида / Ritonavir may increase or interfere with the concentration of glimepiride, lopinavir reduces the effect of glimeperide	Снижается эффект глимепирида / Glimepiride effect is reduced			

	Мефлохин/ mefloquine	Хлорохин/ chloroquine	Гидроксихлорохин / Hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ritonavir	Дарунавир/ darunavir	Рибавирин/ ribavirin	Барицитиниб/ baricitinib	Сарилумаб/ sarilumab
Метформин / Metformin				Ритонавир снижает эффект метформина, риск гипергликемии / Ritonavir reduces the effect of metformin, the risk of hyperglycemia	Снижается эффект метформина / Metformin effect is reduced			
Салметерол / Salmeterol	Риск удлинения QT/ QT interval prolongation			Увеличивается концентрация сальметерола, риск удлинения QT / Salmeterol concentration increases, QT interval prolongation	Увеличивается концентрация сальметерола, риск удлинения QT / Salmeterol concentration increases, QT interval prolongation			
Кларитромицин / Clarithromycin	Увеличивается концентрация мефлохина / Mefloquine concentration increases	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация лопинавира/ ритонавира / Lopinavir/ritonavir concentration increases	Увеличивается концентрация кларитромцина / Clarithromycin concentration increases			
Азитромицин / Azithromycin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация ритонавира, увеличивается токсичность лопинавира, риск удлинения QT / Ritonavir concentration increases, the toxicity of lopinavir increases, the risk of QT prolongation	Риск удлинения QT/ QT interval prolongation			
Левофлоксацин/ levofloxacin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation			
Моксифлоксацин/ moxifloxacin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation			
Метронидазол/ metronidazole	Увеличивается концентрация мефлохина / Mefloquine concentration increases			Увеличивается концентрация лопинавира/ ритонавира / Lopinavir/ritonavir concentration increases	Увеличивается концентрация метронидазола/ Metronidazole concentration increases			

	Мефлохин/ mefloquine	Хлорохин/ chloroquine	Гидроксихлорохин / Hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ritonavir	Дарунавир/ darunavir	Рибавирин/ ribavirin	Барицитиниб/ baricitinib	Сарилумаб/ sarilumab
Триметоприм/ сульфаметоксазол	Риск удлинения QT/ QT interval prolongation							
Флуконазол/ Fluconazole	Увеличивается концентрация мефлохина / Mefloquine concentration increases		Риск удлинения QT/ QT interval prolongation		Увеличивается концентрация дарунавира/ Darunavir concentration increases			
Кетоконазол/ Ketoconazole	Увеличивается концентрация мефлохина, риск удлинения QT/ Mefloquine concentration increases, QT interval prolongation			Увеличивается концентрация кетоконазола/ Ketoconazole concentration increases	Увеличивается концентрация дарунавира, кетоконазола, использовать низкие дозы/ Darunavir, ketoconazole concentration increases,use low doses			
Итраконазол/ Itraconazole	Увеличивается концентрация мефлохина, риск удлинения QT/ Mefloquine concentration increases, QT interval prolongation			Увеличивается концентрация интраконазола/ Intraconazole concentration increases	Увеличивается концентрация дарунавира., использовать низкие дозы/ Darunavir concentration increases,use low doses			
Вориконазол/ Voriconazole	Увеличивается концентрация мефлохина/ Mefloquine concentration increases		Риск удлинения QT/ QT interval prolongation	Уменьшается концентрация вориконазола/ Voriconazole concentration discreases	Darunavir concentration increases/ Увеличивается концентрация дарунавира			
Парацетамол/ Paracetamol	Риск метгемоглобинемии/The risk of methemoglobinemia	Риск метгемоглобинемии/The risk of methemoglobinemia	Риск метгемоглобинемии/The risk of methemoglobinemia					
Колхицин/ Colchicine				Увеличивается концентрация колхицина/ Colchicine concentration increases	Увеличивается концентрация кохицина/ Colchicine concentration increases			
Цетиризин/ Cetirizine				Увеличивается уровень цетиризина/ Cetirizine concentration increases				
Лоратадин/ Loratadine		Увеличивается уровень лоратадина/ Loratadine concentration increases		Увеличивается концентрация лоратадина, ритонавира/ Loratadine, ritonavir concentration increases	Loratadine concentration increases			

	Мефлохин/ mefloquine	**Хлорохин/ chloroquine**	**Гидроксихлорохин / Hydroxychloroquine**	**Лопинавир/ ритонавир/ lopinavir/ritonavir**	**Дарунавир/ darunavir**	**Рибавирин/ ribavirin**	**Барицитиниб/ baricitinib**	**Сарилумаб/ sarilumab**
Дексаметазон/ Dexamethazone				Уменьшается концентрация лопинавира/ Lopinavir concentration discreases	Увеличивается концентрация дексаметазона, снижается концентрация дарунавира/ Dexamethazone concentration increases, darunavir concentration discreases			
Флутиказон / Fluticasone				Увеличивается концентрация флутиказона / Fluticasone concentration increases	Увеличивается концентрация флутиказона / Fluticasone concentration increases			
Беклометазон / Beclometasone				Возможно развитие системных побочных эффектов беклометазона / Perhaps the development of systemic side effects of beclomethasone				
Такролимус/ Tacrolimus	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация такролимуса/ Tacrolimus concentration increases	Усиление иммуносупрессивного эффекта, риск инфекций, риск удлинения QT/ Increased immunosuppressive effect, risk of infections, risk of QT prolongation	Увеличение концентрации такролимуса, конроль концентрации/ Tacrolimus concentration increases	Увеличивается концентрация такролимуса, конроль концентрации/ Tacrolimus concentration increases		Риск развития аддитивной иммуносупрессии/ risk of additive immunosuppressive	
Сиролимус/ Sirolimus			Усиление иммуносупрессивного эффекта, риск инфекций/ Increased immunosuppressive effect, risk of infections	Увеличение концентрации сиролимуса, конроль концентрации/ Sirolimus concentration increases	Увеличивается концентрация сиролимуса, конроль концентрации/ Sirolimus concentration increases			
Циклоспорин/ Cyclosporine	Увеличивается концентрация мефлохина/ Mefloquine concentration increases	Увеличивается концентрация циклоспорина/ Cyclosporine concentration increases	Усиление иммуносупрессивного эффекта, риск инфекций/ Increased immunosuppressive effect, risk of infections	Увеличение концентрации циклоспорина, конроль концентрации/ Cyclosporine concentration increases	Увеличивается концентрация дарунавира, циклоспорина/ Darunavir, cyclosporine concentration increases		Риск развития аддитивной иммуносупрессии/ risk of additive immunosuppressive	

	Мефлохин/ mefloquine	**Хлорохин/ chloroquine**	**Гидроксихлорохин / Hydroxychloroquine**	**Лопинавир/ ритонавир/ lopinavir/ritonavir**	**Дарунавир/ darunavir**	**Рибавирин/ ribavirin**	**Барицитиниб/ baricitinib**	**Сарилумаб/ sarilumab**
Кветиапин / Quetiapine	Риск удлинения QT/ QT prolongation risk	Риск удлинения QT/ QT prolongation risk	Риск удлинения QT / QT prolongation risk	Увеличивается концентрация кветиапина / Quetiapine concentration increases	Увеличивается концентрация кветиапина / Quetiapine concentration increases			
Карбамазепин/ Carbamazepine				Уменьшается концентрация лопинавира/ Lopinavir concentration discreases	Уменьшается концентрация дарунавира, увеличивается концентрация карбамазепина/ Darunavir concentration discreases, carbamazepine concentration increases			
Фенобарбитал/ Phenobarbital	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia	Уменьшается концентрация лопинавира/ Lopinavir concentration discreases	Уменьшается концентрация дарунавира/ Darunavir concentration discreases			
Фенитоин/ Phenytoin				Уменьшается концентрация лопинавира/ Lopinavir concentration discreases	Уменьшается концентрация дарунавира/ Darunavir concentration discreases			
Вальпроевая кислота/ Valproic acid	Уменьшается концентрация вальпроевой кислоты/ concentration discreases			Снижается концентрация вальпроевой кислоты, контроль концентрации / concentration discreases				
Ламотриджин/ Lamotrigine				Снижается концентрация ламотриджина, контроль концентрации / Lamotrigine concentration discreases				

Клинически значимых взаимодействий не ожидается	Возможны взаимодействия, применять с осторожностью	Риск развития нежелательных реакций, применять под контролем	Избегать совместного назначения, высокий риск осложнений
No clinically significant interactions expected	Possible interactions, use with caution	Risk of adverse reactions, apply under control	Avoid co-administration, high risk of complications

Risk factors for infections related to tocilizumab include: age (over 50 years), obesity (body mass index (BMI) more than 30 kg/m^2), history of immunosuppressive treatment, concomitant immunosuppressive treatment (including glucocorticosteroids — GCSs), administration of high doses of the drug, chronic lung diseases and diabetes mellitus [51]. For tocilizumab and sarilumab, transient dose-dependent neutropenia is a typical side effect that does not increase the risk of severe infections [52, 53]. Studies involving patients with rheumatoid arthritis demonstrated that the risk of the following infections usually increases: infections of the upper and lower respiratory tract, urinary tract, skin and soft tissues [54, 55]. A higher risk of fungal, viral infections, and tuberculosis should also be noted [56–58]. The risk of severe infections related to the short-term use of tocilizumab and sarilumab is not fully understood. However, it should be considered as a possible risk factor for bacterial and fungal complications in patients with severe viral pneumonia in combination with other factors.

Hepatotoxicity is a typical side effect of tocilizumab and sarilumab, which manifests as an increase in hepatic transaminases. The mechanism is not clear; it may be the result of inhibition of IL-6, which plays an important role in liver regeneration. There have been reports of acute liver failure related to tocilizumab, which required liver transplantation. There are no major hepatic complications related to sarilumab [59]. Drugs should be prescribed while monitoring hepatic enzymes. Co-administration with other hepatotoxic drugs should be avoided; they should be used with caution in patients with impaired liver function. There have been reports of acute pancreatitis related to tocilizumab. This fact should be considered when starting treatment [60].

The risk of perforation and bleeding from the gastrointestinal tract (GIT) related to IL-6 inhibitors [61] should be noted since their use can be indicated for patients in intensive care units who are already at a high risk of stress ulcers [62]. Risk factors for GIT complications include elderly age, oral administration of GCSs, nonsteroidal anti-inflammatory drugs (NSAIDs) and a history of diverticulitis [63]. There is an observation describing the development of inflammatory foci in GIT after the first administration of tocilizumab and the development of multiple perforations and bleeding eight days after its repeated administration in a 15-year-old patient [64]. The mechanism of damage is not fully understood, but it may be associated with the suppression of immune response and the effect on the vascular endothelial growth factor [65].

Interferon Beta-1b

A common side effect of interferon beta-1b is an influenza-like syndrome that manifests as fever, chills, and headache and can be mistakenly interpreted as deterioration during treatment of acute viral infection [66].

Possible side effects of interferon beta-1b may be mental disorders (onset or exacerbation of depression, suicidal thoughts, psychosis), but they typically appear when treatment lasts at least two months [67].

Liver injury that manifests as a transient increase in hepatic transaminases to 3–5 upper normal limits (UNL) is quite common, unlike severe injuries that are less common [68].

Baricitinib

Taking into account the primary mechanism of action of baricitinib — selective inhibition of type 1 and 2 Janus kinases — that results in immunosuppressive action, its administration can raise the risk of infectious complications. Studies conducted in a group of patients with rheumatoid arthritis showed a high risk of upper respiratory tract and urinary tract infections, and Herpes Zoster reactivation. Among the risk factors were the administration of corticosteroids, a history of biological drug treatment, insufficient or excessive BMI, and elderly age [69].

There was a slight increase in the blood creatinine level two weeks after starting barcitinib therapy, which may be associated with the inhibition of tubular creatinine secretion by the drug. There was also a transient — without clinical signs — increase in phosphocreatine kinase to 5 UNL and hepatic transaminases to 3–5 UNL [70].

Anti-inflammatory drug ketorolac and antihypertensive drug valsartan (angiotensin II receptor antagonist) increase baricitinib concentration,

which increases the risk of adverse reactions. Therefore, their combined use should be avoided. The combined use of baricitinib and tocilizumab may increase the risk of infectious complications by intensifying the immunosuppressive effect.

Low-Molecular-Weight Heparin

Anticoagulant treatment or prevention with low-molecular-weight heparin (LMWH) is recommended for all hospitalized patients without contraindications since it was noted that hypercoagulation syndrome is typical for COVID-19 patients [19, 71].

The main side effect of LMWH, as well as of other anticoagulants, is bleeding of various severity, which requires the monitoring of anti-Xa activity and renal function. The combined use of enoxaparin and dalteparin with antibacterial drugs such as macrolides (azithromycin, erythromycin), certain cephalosporins (cefazolin, cefoxitin, cefuroxime, ceftriaxone), piperacillin, and sulfamethoxazole can increase the risk of bleeding.

Decreased platelet count related to heparin and less commonly LMWH may be a sign heparin-induced thrombocytopenia (HIT), which is a contraindication for the use of heparin drugs. There are two types of HIT: type 1 is due to the direct effect of the drug on platelets, it usually manifests in the first three days of use, disappears spontaneously, does not increase the risk of thrombosis; type 2 is due to immune response, usually manifests up to 14 days from the beginning of treatment, increases the risk of thrombosis [72, 73]. Type 2 HIT is of high clinical significance: platelet level decreases by more than 50% from the baseline; manifests in arterial and venous thromboses of different localization. Risk factors for HIT include high (therapeutic) doses of unfractionated heparin, use after surgery or injury, female sex [74, 75]. If HIT is suspected or confirmed, it is required to switch to alternative drugs, for example, fondaparinux sodium.

Oral Anticoagulants

Oral anticoagulants are not recommended for the prevention of thromboembolic complications in COVID-19 patients, but their continued use is allowed for patients who take these drugs according to other indications if the disease is mild [19]. However, it is worth remembering possible interactions with other drugs that are recommended for the treatment of coronavirus infection since they can significantly increase the blood concentration of anticoagulants and cause bleeding [76].

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

There is an intense debate over the role of angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) in the development and evaluation of the severity of novel coronavirus infection. This is due to the ability of the virus to bind to the extracellular domain of type 2 transmembrane angiotensin-converting enzyme receptor (ACE2), which leads to the infection of target cells. It was established that the ACE2 expression level is highest in the small intestines, kidneys, heart, thyroid gland, and adipose tissue; average — in the lungs, large intestines, liver, bladder, and adrenal glands; and lowest — in the spleen, bone marrow, brain, blood vessels, and muscles [77]. In animal models, there was an increase in ACE2 expression during the administration of ACEI and ARB. There are currently no reliable data on changes in this expression in humans [78].

Due to fears of a more severe course of novel coronavirus disease when taking ACE inhibitors and ARBs, several authors recommended to stop taking these drugs, which are crucial in the complex treatment of many chronic diseases. In response, professional associations such as the American Heart Association, American College of Cardiology, the Heart Failure Society of America, European Society of Cardiology, and the Russian Society of Cardiology recommend continuing treatment with the above drugs due to the lack of convincing clinical and experimental data on the deterioration of the course of COVID-19. In addition, the refusal of treatment significantly increases the risk of cardiovascular events, which complicates the course of coronavirus disease. Hence, it is also not recommended to

start treatment with ACEI/ARB in patients without clinical indications (hypertension, heart failure, and diabetes mellitus) [79].

A pilot study using recombinant human ACE2 (APN01) in patients with COVID-19 is underway. The administration of APN01 rapidly lowers the levels of angiotensin II and IL-6 in blood plasma, and can also potentially reduce viral load [80].

Therefore, the side effects of drugs that are currently used against COVID-19 infection vary and are potentially significant. However, they can be significantly minimized by taking into account the risks of their development and possible adverse interactions.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

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