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Review Article

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COVID-19 and chronic kidney disease: peculiarities of treatment

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Abstract. *The present study aimed to characterize the management of patients with chronic kidney disease with concomitant COVID-19. Articles published in 2019-2021 in the PubMed, Scopus, and Google Scholar electronic databases were analyzed.*

As a result of this review, the following particularities of COVID-19 treatment in chronic kidney disease could be summarized. It is obligatory to continue treatment with renin-angiotensin-aldosterone system inhibitors in patients with chronic kidney disease and COVID-19. Lisinopril is considered used for avoiding the elevated renal expression of angiotensin-converting enzyme 2. Spironolactone can prevent acute lung injuries and is reasonable if the triple combination of drugs for reducing blood pressure is not effective. Low-dose rosuvastatin therapy is recommended for patients with COVID-19 and chronic kidney disease stages 3-5 treated with antiretroviral drugs such as lopinavir and ritonavir, remdesivir. Ezetimibe is reasonable to use in case of ineffective higher doses of statins and to decrease hospitalization risk.

Keywords: *chronic kidney disease, COVID-19, statins, angiotensin-converting enzyme inhibitors.*

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COVID-19 та хронічна хвороба нирок: особливості лікування.

Огляд літератури.

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Резюме. Метою цього дослідження було охарактеризувати особливості лікування пацієнтів із хронічною хворобою нирок та супутнім COVID-19. Проаналізовано статті, опубліковані у 2019-2021 роках в електронних базах PubMed, Scopus та Google Scholar.

У результаті цього огляду можна підсумувати наступні особливості лікування COVID-19 у хворих на хронічну хворобу нирок. Обов'язковим є продовження лікування інгібіторами ренін-ангіотензин-альдостеронової системи; вважається, що лізиноприл використовується для уникнення підвищеної ниркової експресії ангіотензинперетворюючого ферменту 2. Спіронолактон може запобігти гострому ушкодженню легень і є доцільним у разі неефективності потрійної комбінації гіпотензивних лікарських засобів. Терапія низькими дозами розувастатину рекомендована пацієнтам із COVID-19 та хронічною хворобою нирок 3-5 стадії, які лікуються антиретровірусними засобами, такими як лопінавір та ритонавір, ремдесивір. Езетиміб доцільно застосовувати у разі неефективності високих доз статинів та з метою зниження ризику госпіталізації.

Ключові слова: хронічна хвороба нирок, COVID-19, статини, інгібітори ангіотензин-перетворюючого ферменту.

Patients with chronic kidney disease (CKD) have an increased risk of COVID-19 infection [1, 2], its severe course, and mortality [3]. A decreased glomerular filtration rate (GFR) is associated with a higher risk of COVID-19-related death [4]. Moreover, the coexistence of CKD and SARS-CoV-2 infection is characterized by an increased risk of cardiovascular events [5].

On the one hand, SARS-CoV-2 provokes acute kidney injury [6]. The increase of serum creatinine and blood urea nitrogen, and the appearance of hematuria and proteinuria were determined in 701 patients with COVID 19 in China [3]. On the other hand, CKD is associated with an increased risk of severe COVID-19 infection [3, 7]. A majority of CKD patients have coexistent diabetes mellitus and hypertension that significantly increase the risk of COVID-19 infection [3, 7]. Endothelial dysfunction, microangiopathy, coagulation disorders [8] and imbalance of the renin-angiotensin-aldosterone system (RAAS) are the key links to kidney damage in the case of such comorbidity [9].

According to Bitencourt et al, early-stage CKD patients had a worse prognosis of COVID-19 compared with end-stage kidney disease (ESKD) patients [9]. The authors have concluded that hemodialysis patients have mild severity of COVID-19 because of a lower risk of being affected by the cytokine storm [9]. However, hemodialysis patients are immunosuppressed and have

to constantly visit their dialysis centers that are predisposed to infections [10-13].

Collado S. et al. have determined COVID-19 treatment prognosis in CKD patients in stages 4 and 5 and described that bilateral pneumonia was confirmed in 5 patients treated with hydroxychloroquine, azithromycin, ceftriaxone and steroids [14]. Six patients continued dialysis and a 76-year-old patient died [14].

Dudar I. et al. have assessed the incidence of COVID-19 among dialysis patients and found that only 20% of hemodialysis patients had been affected with COVID-19 while peritoneal dialysis had a significantly lower incidence than hemodialysis [15]. Severe COVID-19 was confirmed in dialysis patients with coexistent obesity and cardiovascular diseases. Furthermore, the association between COVID-19 severity, the patients' age and dialysis vintage has not been defined [15].

Treatment with remdesivir in CKD patients is still controversial. Some investigators do not prescribe remdesivir as routine treatment in CKD patients with COVID-19 and GFR less than 30 ml/min/1.73 m² [16]. Other researchers recommended a 5-day course of remdesivir in CKD patients with GFR less than 30 ml/min/1.73 m² and determined that it is safe. In the opinion of Adamsick ML et al., patients with COVID-19 who have impaired renal function should be offered remdesivir treatment due to its potentially life-saving effect [17].

Some hypothetical benefits and harms have been suggested for statins and RAAS inhibitors in patients with COVID-19 [18]. The use of RAAS blockers is associated with reducing albuminuria and is recommended as part of the treatment strategy in hypertensive patients [19]. The membrane-bound angiotensin-converting enzyme II (ACE2) is the receptor for SARS-CoV-2 that

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predisposes to an imbalance of the RAAS, and worse clinical features of COVID-19.

ACE2 receptors expressed by kidney proximal tubules are the major binding site for SARS CoV 2 which enters the host cell through binding to them [20]. This receptor is presented by epithelial cells of the lungs, intestine, kidney and blood vessels [21]. As a result, the first step of SARS-CoV-2 infection in humans is the contact of the virus with cell-surface ACE2. The last one interacts with external SARS-CoV-2 by binding to the receptor-binding domain of the viral spike protein [8]. Once in the cytoplasm, SARS-CoV-2 releases its genomic RNA and starts replicating inside the podocytes resulting in proteinuria [3].

According to the conclusion of Hakeam HA et al., patients with arterial hypertension or cardiovascular diseases treated with RAAS inhibitors on the day of hospital admission or continued ACE inhibitors/angiotensin II receptor blockers (ARBs) therapy during hospitalization, did not have an increased risk of severe COVID-19 [22]. Besides, discontinuation of these medications was associated with the worsening of cardiac failure and death [23]. Opposite, ACE inhibitors/ARBs have been shown to increase ACE 2 receptor expression in the tissues infected by SARS CoV 2 [24, 25]. It has been demonstrated that increased ACE 2 expression might facilitate viral cellular infection contributing to the SARS CoV 2 endotheliopathy development [26], which can provoke the increased incidence of kidney disorders, thrombosis and mortality [25]. The key link between hypertension and COVID-19 is ACE2 [27]. An increase in ACE activity, intensification of oxidative processes, and decrease of antioxidant defense contribute to the development of local oxidative stress, as well as the development of dysfunction in the renal tubular system (according to the increased activity of renal specific enzymes in the urine) [28].

It has been shown that the use of ACE inhibitors and (ARBs) in the treatment of diabetes mellitus and hypertension including in CKD patients increased the risk of severe and fatal COVID-19 [29, 30]. However, Reynolds HR et al. have demonstrated that there was no relationship between RAAS inhibitors and an increased likelihood of a positive COVID-19 test [31]. The same conclusion was made by Mancina G et al. who determined the absence of association between these medications and the risk of SARS-CoV-2 infection [32]. According to the mentioned preclinical studies, there was no consistent evidence that the use of RAAS inhibitors leads to an increase in ACE2 expression during COVID-19. Diabetics with CKD and/or arterial hypertension should not discontinue using ACE inhibitors and ARBs [33-37]. Hakeam et al. have suggested that lisinopril and losartan were the most frequently used ACE inhibitors in patients with COVID-19 [22].

In preclinical studies, telmisartan [38] and olmesartan [39] significantly increased cardiac ACE2 expression. Candesartan increases ACE2 activity twice in diabetes [40]. In the kidney context, azilsartan [41]

and lisinopril [42] did not increase renal ACE2 expression.

It has been established that patients with hypertension are at different stages of psychoemotional stress that predispose them to complications [43]. In hypertension patients, including those with CKD, the triple combination of drugs for reducing blood pressure was not effective and spironolactone prescribed in a dose of 25–50 mg per day was recommended to add [19]. Spironolactone tends to disclose favorable patterns of the RAAS and ACE2 expression, reduce transmembrane serine protease 2 activities due to its antiandrogenic activity, and may prevent acute lung injuries due to its pleiotropic effects [44]. In this context, the protective effect of spironolactone might be realized in severe COVID-19 patients with obesity and hypertension [44].

Statins are well-known lipid-lowering medications with a huge number of pleiotropic effects [45, 46]. They are used for the treatment of COVID-19 and can reduce pro-inflammatory cytokines such as interleukins and tumor necrosis factor-alpha [45] that are associated with the progression of CKD [47]. In addition to improvement of cardiovascular disease outcomes [48-50], lipid-lowering therapy has been demonstrated to improve coagulopathy, and endothelial function, and reduce inflammation [46, 51, 52]. Low-dose rosuvastatin therapy was recommended in patients COVID-19 patients treated with antiretroviral drugs (lopinavir/ritonavir) [53]. Lovastatin and simvastatin are contraindicated in such patients because of the increased risk of rhabdomyolysis [54]. Atorvastatin, simvastatin, and lovastatin should be avoided in patients treated with remdesivir that is connected with the Cyp3A4 pathway of metabolism [53]. Ezetimibe and rosuvastatin were associated with reduced SARS-CoV-2 hospitalization risk in general and dialysis populations [46, 55].

Severe pulmonary infiltration, edema and inflammation lead to impaired alveolar homeostasis, pulmonary fibrosis, endothelial disorders and vascular thrombosis in patients with COVID-19-associated acute respiratory distress syndrome [56]. Severe pulmonary involvement in COVID-19 is associated with high comorbidities and, accordingly, CKD. ACE inhibitors and ARBs are the first-line therapy for persons with hypertension and albuminuria. These drugs demonstrated the reduction of cardiovascular events and the risk of CKD progression [57]. However, there was no priority in losartan or amlodipine administration in COVID-19 hypertensive patients in decreasing mortality rate and hospitalization [58]. Some investigators suggested that in mild symptomatic COVID-19 losartan did not reduce hospitalizations [59], others concluded that losartan and imatinib are promising in this infection because of decreasing of SARS-CoV2 affinity to ACE2 and inhibition of the main protease [60]. Telmisartan use was associated with a decrease in serum C-reactive protein in urgent and stable hospitalized COVID-19 patients resulting in the reduction of the clinical symptoms [61]. Valsartan treatment did not significantly impact the ex-

pression of ACE2, in human adipose tissue and skeletal muscle [62]. Thus, neither hypertension nor antihypertensive treatment is likely to alter the expression of the key entry receptor for SARS-CoV-2 in the human kidney. Moreover, taking hypotensive medications reported to be safe in younger cohorts, does not contribute significantly to increased COVID-19-related deaths in an older population [63].

In conclusion, lisinopril and telmisartan are recommended for reducing albuminuria, serum C-reactive protein and prevention of severe forms of COVID-19 infection in CKD patients. Rosuvastatin is preferable for CKD stages 3-5 patients with COVID-19 treated

with antiretroviral drugs; ezetimibe is considered as a second step for reduction of SARS-CoV-2 hospitalization risk. Spironolactone should be used to avoid acute lung injuries in CKD patients with COVID-19.

Conflicts of interest: the authors declare no conflict of interest

Authors contribution:

O. Chernatska: the study concept, literature search, data analysis and interpretation, manuscript writing, and was a major contributor in writing the manuscript;

A. Grek: literature search.

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