Chapter 15
Interaction of Anti-COVID-19 Drugs with Cardiovascular Therapy

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In recent years, the world has been facing a major pandemic of the COVID-19 caused by virus called SARS-CoV-2, an infection of which at the beginning we did not know much about. Guidelines have been constantly changing with the development of new vaccines and antiviral drugs. In an emergency of trying to prevent a cytokine storm and an unfavorable outcome of the infection, the interaction with concomitant therapy was often not considered. Due to the different outcomes of patients treated with the same therapy, the possible interaction of drugs gradually began to be widely considered.

Cardiovascular drugs are the most widely used drugs in the world for secondary and primary prevention as well as treatment of cardiovascular diseases (CVD). In addition to targeted effects on blood pressure, heart rate, levels of blood cholesterol, etc., cardiovascular drugs have other secondary, immunomodulatory, and pleiotropic effects that may interfere with other drugs, especially antiviral drugs. In this chapter, we have summarized the most important interactions between some most widely used cardiovascular drug groups and COVID-19 therapy, their benefits and potential adverse effects.

Our focus is based on antiviral and immunomodulatory therapy (corticosteroids, IL-6 and JAK inhibitors, monoclonal antibodies) used in the treatment of COVID-19.

Statins

Statins are drugs that reduce cholesterol levels by inhibiting 3-hydroxy-3methylgultaryl-coenzyme A (HMG-CoA) reductase in the liver cells and are some of the most prescribed drugs worldwide today. They have numerous pleiotropic effects

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including positive effect on the function of vascular endothelium, stabilization of atherosclerotic plaque, anti-inflammatory and anti-proliferative effects. They reduce tissue factor (TF) expression, synthesis of thrombin and platelet activation. Therefore, they have a strong anticoagulant effect [1]. Statins have also immunomodulating role on differentiation, proliferation, and secretion of immune cells (macrophages, lymphocytes T) and a strong anti-inflammatory effect reducing serum C-reactive protein (CRP), tumor necrosis factor α (TNF-α), as well as interleukins 1 and 6 (IL-1, IL-6) [2]. In addition to these effects, it is not surprising that the role of statins became important in COVID-19 which is characterized by cytokine storm and prothrombogenic effect. Studies have shown a significant reduction in the mortality of patients with COVID-19 who were on statin therapy [3–5]. The first indication that statins might have also a direct beneficial effect on SARS-CoV-2 viruses by inhibiting SARS-CoV-2 main protease was published already at the beginning of the 2020 [6].

Statins are mostly metabolized in the liver by CYP3A4, but also to a lesser extent by CYP2C9, CYP2C8, and CYP2D6. The most common adverse effects include muscle pain, and very rarely in severe cases rhabdomyolysis, and even more rarely acute liver and kidney injury [7]. Therefore, statins are contraindicated in the severe form of COVID-19 which is unfortunately often seen in this pandemic. Even in moderate COVID-19 disease, sometimes severe liver lesions often occur in which cases statins should be discontinued despite their beneficial effects.

During therapy with antiviral agents, such as remdesivir (inhibitor of RNA-dependent RNA polymerase), the dose of statins needs to be adjusted with frequently monitoring of hepatic and renal function. Remdesivir is an inhibitor of CYP3A4 enzyme and therefore it might increase the toxicity of drugs such as statins that are metabolized by this enzyme [8]. Based on clinical studies, it is recommended to reduce the dosage of rosuvastatin and atorvastatin on the lowest possible and often monitor liver enzymes and creatine kinase levels. Lovastatin and simvastatin should be avoided when using remdesivir, and the dosage of atorvastatin or rosuvastatin should not exceed 20 mg/day.

Tocilizumab, a humanized monoclonal antibody that inhibits interleukin 6 receptor α, is indicated in the severe form of COVID-19 (worsening of the clinical condition, progression of hypoxemia, hypercytokinemia). Many studies have shown that the use of tocilizumab adversely affects the lipid profile, i.e. it increases the concentration of total cholesterol, LDL-cholesterol, and triglycerides which further increases cardiovascular risk and the chance thromboembolic events in COVID-19 [9]. Also, studies have shown that concomitant statin therapy reduces the shift in lipid profile during tocilizumab therapy without the risk of major adverse events [10]. Nevertheless, it is important to emphasize that regular monitoring of liver enzymes is necessary, and if ten-fold increase in liver transaminases occurs, tocilizumab is contraindicated.

Corticosteroids (dexamethasone, prednisone, prednisolone, and methylprednisolone) are the basic therapy in preventing cytokine storm during COVID-19. They have strong anti-inflammatory and immunomodulatory effects and act synergistically with statins.

Nevertheless, corticosteroids are inducers of CYP3A4 enzymes. Therefore, the potential toxicity of statins should be monitored.

According to some studies, statin therapy is not contraindicated with the use of monoclonal antibodies such as casirivimab/imdevimab combination or monotherapy with regdanvimab and sotrovimab.

β-Blockers

The cardioprotective effect of β-blockers in COVID-19 is well known. Numerous studies have shown a beneficial effect on sympathetic and cytokine storms that endanger patients mostly [11]. The main beneficial effects include reduction of sympathetic stimulation, pro-inflammatory cytokines, cardiac arrhythmia and cardiac injury. Non-selective β-blockers appear to be more effective due to inhibition of excessive immune response via β2-adrenoreceptors expressed in the airways. On the other hand, selective β-blockers have less adverse effects including bronchospasm and peripheral vasoconstriction. The metabolism of β-blockers depends on the pathway of elimination. Lipophilic β-blockers are completely metabolized by liver, especially by CYP2D6 enzymes. Therefore, slow metabolizers can result in adverse events. Hydrophilic β-blockers (atenolol, bisoprolol, nadolol, and sotalol) are eliminated by kidneys, dependent on glomerular filtration. In acute kidney injury the dosage of the drug should be reduced because of an increased risk of adverse effects.

According to current guidelines and available literature, the use of tocilizumab with beta-blockers during COVID-19 infection is not contraindicated and no interactions have been described. Nevertheless, there are studies on rheumatoid arthritis that indicate a reduced chance of remission with concomitant use of tocilizumab and β-blockers. The proposed mechanism is via β1adrenergic-receptor which inhibit the migration of innate immune cells [12]. In these studies, patients predominantly used selective β-blockers, so further studies are needed to confirm these hypotheses and potential interactions between tocilizumab and β-blockers.

Remdesivir is extensively metabolized by CYP2C8, CYP2D6, and CYP3A4. Therefore, greater caution is required when co-administered with β-lockers [13]. Metoprolol, carvedilol, and bisoprolol are metabolized by CYP2D6 which is highly polymorphic causing different phenotypes of metabolizer. Studies show that 20% of European and 40% of Asian patients have functional polymorphism of CYP2D6 resulting in decreased function and β-blockers intolerance (hypotension, bradycardia, and bronchospasm) [14]. Therefore, dose reduction or discontinuation of therapy should be considered in patients with these adverse events. Despite this, large multicenter studies have not found an association between severe bradycardia and concomitant use of remdesivir and beta-blockers in hospitalized patients with COVID-19 [15]. On the other side, there is a potentially harmful interaction between atazanavir and β-blockers (propranolol, atenolol) due to an additive PR interval prolongation resulting in irregular heart rhythm. Therefore, concomitant use of these two drugs is contraindicated [16].

The synergistic beneficial effect of corticosteroids and β-blockers against cytokine storm is well known, but caution should be advised with prolonged usage of corticosteroids since worsening of arterial hypertension may occur. This effect is described when using prednisone with propranolol since corticosteroids are involved in regulating balance of water and sodium in the body. Nevertheless, β-blocker therapy should not be discontinued because of its strong cardioprotective effect.

Antihypertensive Drugs

Arterial hypertension is one of the most common chronic diseases in the world. The consequences of this disease greatly reduce the quality of life and contribute to an increase in cardiovascular and overall mortality. This is especially important in the era of COVID-19 since studies have shown an association between greater need for ventilatory support in patients with severe COVID-19 infection with arterial hypertension as co-morbidity [17]. According to current guidelines, the first line drugs for arterial hypertension are inhibitors of renin-angiotensin system (RAS): angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) [18]. Clinical studies in the beginning of COVID-19 pandemic indicated an association between SARS-CoV-2 virus and angiotensin-converting enzyme 2 (ACE2), expressed on the surface of alveolar cells in the lungs, suggesting a crucial role of the enzyme for entrance and replication of virus in the cells. This was based upon evidence that ACE2 might be potential cellular receptor for coronavirus spike protein (S-protein). Several in vitro studies have shown an increase in ACE2 levels when using ACEi or ARB. Therefore, there was a great concern about the use of these antihypertensive drugs in COVID-19 patients [19]. Fortunately, a significant number of clinical studies during COVID-19 pandemic excluded the possibility that renin-angiotensin system (RAS)-blocking drugs might increase the level of ACE2 expression in humans [20]. On the contrary, a beneficial therapeutic effect of inhibiting the RAS cascade, a target of ACE2, in patients with COVID-19 and CVD has been suggested [21].

Nevertheless, the discovery of new drugs against COVID-19 has opened up the possibility of drug–drug interaction which potentially could endanger patient's health. This is especially important for the antihypertensive drugs since antihypertensives from several groups are often taken at the same time (fixed combination of RAS-blockers and calcium channel blockers or diuretics).

Clinical studies show that corticosteroids (especially dexamethasone) interact with all groups of antihypertensive drugs, reducing their antihypertensive effect due to their effect on water and sodium balance. Since corticosteroids are the first line treatment for the severe COVID-19, blood pressure needs to be measured more frequently to prevent hypertensive crises. In hypertensive crises during COVID-19 the use of strong vasodilators (e.g., nitroprusside) is recommended.

Although most antihypertensives do not show interactions with antiviral drugs, some interactions have been described. Combining calcium channel blocker

(amlodipine) with antiviral drug atazanavir could prolong PR interval resulting in arrhythmia and cardiotoxicity.

Caution should also be exercised when using nirmatrelvir/ritonavir with amlodipine since these drugs enhance plasma amlodipine concentration resulting with hypotension [22]. So far, the interaction between remdesivir and antihypertensive drugs is not described. Therefore, remdesivir can be used in patients with severe arterial hypertension.

Most monoclonal antibodies against COVID-19 infection do not interact with antihypertensive drugs and therefore their use is safe. These are casirivimab/imdevimab, etesevimab/bamlanivimab, and sotrovimab approved by Food and Drug Administration (FDA). Tocilizumab, on the other hand, interferes with amlodipine by affecting the drug-metabolizing enzymes like CYP3A4 whose substrate is amlodipine [23].

With the development of new drugs targeting the SARS-CoV-2 virus, possible interactions with concomitant therapy, especially cardiovascular drugs, need to be considered. Cardiovascular drugs should be able to be administered in full dose even in the severe forms of COVID-19 because the disease itself increases cardiovascular risk. Therefore, the development of new anti-COVID19 drugs that do not interact with concomitant therapy would be a step further in the fight against this pandemic.

Natural Drugs

It must be mentioned that some natural products might be effective against SARS-CoV-2 since it is known that some dietary supplements, including black seeds, garlic, ginger, cranberry, orange, omega-3 and -6 polyunsaturated fatty acids, vitamins (e.g., A, B vitamins, C, D, E), and minerals (e.g., Cu, Fe, Mg, Mn, Na, Se, and Zn) have antiviral effects. Therefore, they might be used as adjuvant therapy together with antiviral medicines in the management of COVID-19 disease, particularly in patients with CVD, but more clinical studies are needed to prove beneficial effect [24, 25]. Since they were not thoroughly studied in combination with anti-COVID-19 drugs, not much is known about possible interactions between them.

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