

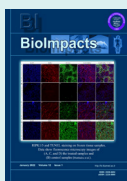
Antiviral and anti-inflammatory drugs to combat COVID-19: Effects on cardiac ion channels and risk of ventricular arrhythmias

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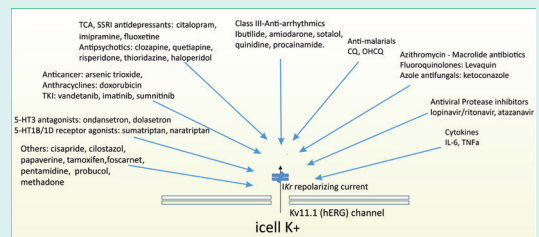
Abstract

Introduction: Drugs with no indication for the treatment of cardiovascular diseases (e.g., drugs employed to treat COVID-19) can increase the risk of arrhythmias. Of interest, a six-fold increase in the number of arrhythmic events was reported in patients with severe COVID-19. In this study, we reviewed (i) the pro-arrhythmic action of drugs given to patients with COVID-19 infection, and (ii) the effects of inflammatory cytokines on cardiac ion channels and possible generation of arrhythmias.

Methods: We conducted a literature search on the drugs with purported or demonstrated efficacy against COVID-19 disease, emphasizing the mechanisms by which anti-COVID-19 drugs and inflammatory cytokines interfere with cardiac ion channels.

Results: Antibiotics (azithromycin), antimalarials (hydroxychloroquine, chloroquine), antivirals (ritonavir/lopinavir, atazanavir), and some of the tyrosine kinase inhibitors (vandetanib) could induce long QT and increase risk for ventricular arrhythmias. The pro-arrhythmic action results from drug-induced inhibition of Kv11.1 (hERG) channels interfering with the repolarizing potassium *IKr* currents, leading to long QT and increased risk of triggered arrhythmias. At higher concentrations, these drugs may interfere with *IKs*, *IK1*, and/or *Ito* potassium currents, and even inhibit sodium (*I_{Na}*) and calcium (*I_{Ca}*) currents, inducing additional cardiac toxicity. Ibrutinib, an inhibitor of Bruton's TK, increased the incidence of atrial fibrillation and ventricular tachycardia associated with a short QT interval. Inflammatory cytokines IL-6 and TNF- α inhibit *IKr* and *Ito* repolarizing potassium currents. High levels of inflammatory cytokines could contribute to the arrhythmic events. For remdesivir, favipiravir, dexamethasone, tocilizumab, anakinra, baricitinib, and monoclonal antibodies (bamlanivimab, etesevimab, and casirivimab), no evidence supports significant effects on cardiac ion channels, changes in the QT interval, and increased risk for ventricular arrhythmias.

Conclusion: This study supports the concept of hERG channel promiscuity. Different drug classes given to COVID-19 patients might delay repolarization, and increase the risk of ventricular arrhythmias. The presence of comorbid pro-arrhythmic disease states, and elevated levels of pro-arrhythmic cytokines, could increase the risk of ventricular arrhythmias. Discontinuation of nonessential drugs and correction of electrolyte abnormalities could prevent severe ventricular arrhythmias. Altogether, the most effective therapies against COVID-19 (remdesivir, dexamethasone, monoclonal antibodies) lack pro-arrhythmic activity.



Introduction

The severe acute respiratory syndrome caused by the new β -coronavirus named SARS-CoV-2, later labeled by the World Health Organization (WHO) as COVID-19, has reached pandemic proportions.¹ As of January 10, 2021, approximately 89 million subjects worldwide were reported infected with COVID-19, with 50 million patients recovered and 1.9 million deceased; a number

that increased to 228 million and 4.6 million, respectively, by September 21, 2021.¹ The clinical presentation of COVID-19 infection varies from asymptomatic, to mild, moderate, and severe, and even death.² Besides the direct pathogenic actions of SARS-CoV-2 and its variants, an abnormal inflammatory, immune, and pro-coagulant response determines the severe course of the disease.³ Due to the lack of effective treatments to treat



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severe COVID-19, the FDA issued compassionate and emergency use authorizations of drugs and antibodies to treat this novel disease. Consequently, early during the pandemic, patients received treatments whose proposed efficacy relied on *in vitro* antiviral activity, and on prior use in inflammatory and autoimmune diseases. A wide range of compounds, with different chemical structures and mechanisms of action, were and are being used, either alone or in combination, in an attempt to cure or minimize disease severity.^{4,6} The list includes antibiotics (azithromycin, doxycycline), antimalarials (hydroxychloroquine, chloroquine), antivirals (ritonavir/lopinavir, remdesivir, favipiravir), anti-inflammatory drugs such as steroids (dexamethasone), IL-6 antagonists (tocilizumab), interleukin-1 (IL-1) antagonists (anakinra), June kinase-JAK1 and JAK2 inhibitors (baricitinib), tyrosine kinase inhibitors (TKIs) (ibrutinib), and monoclonal antibodies (bamlanivimab, etesevimab, casirivimab, and imdevimab). We learned that many of these agents were ineffective, with a high risk-to-benefit ratio. As of today, remdesivir and dexamethasone gained FDA approval, while monoclonal antibodies and baricitinib are under EUA.

Old age, hypertension, obesity, diabetes, cardiovascular disease, chronic lung disease, and immunosuppression predict the severe course of COVID-19, risk of hospitalization, admissions to ICU, and mortality.² Besides, associated comorbidities require additional drug therapies, often in high doses, increasing the risk of drug-induced toxicity. Several of the anti-COVID19 drugs interfere with cardiac ion channels, and their use is associated with severe ventricular arrhythmias^{4,6} (Table 1, Fig. 1). Moreover, the pro-arrhythmic potential of drugs increases in patients with comorbidities known to predict severe disease.⁷⁻⁹ In addition, in hospitalized COVID-19 patients, 16.7% experienced arrhythmias. Patients that were admitted to the ICU due to more severe illness had a greater incidence of arrhythmias than the non-ICU patients (44.4% vs 6.9%).¹⁰ Because of its clinical relevance, we investigated the potential pro-arrhythmic action of drugs used in the treatment of COVID-19. Here, we discuss the cardiac channels and ion fluxes affected, and the mechanisms of channel inhibition when available, for drugs that were and are used to treat COVID-19 disease, including the role of inflammatory cytokines.

Torsade de Pointes, cardiac potassium-ion channels, long QT and SCD

Torsade de Pointes (TdP) is the most common cause of drug-induced ventricular tachycardia and sudden cardiac death (SCD). TdP presents as a polymorphic ventricular tachycardia, commonly most often accompanied by a long QTc interval. TdP most often results from inhibition of the *IKr* potassium currents conducted through the human ether-a-go-go-related gene (hERG) channels.^{4,9} Multiple, structurally different drugs act upon the hERG channel

to inhibit *IKr*, (Fig. 1), prolonging repolarization. This manifests with widening the ventricular action potential, long QT, increased risk of afterdepolarizations, and ventricular arrhythmias. The long QTc is often associated with greater QT dispersion, irregularities of the T waves, presence of U waves, and of T wave alternant, which further increases the risk of developing TdP.¹¹

Ion channels are composed of alpha-subunits that are the pore-forming section of the channel. The alpha subunits together with the beta-subunits and other proteins form a complex, which regulates the channel activity. There are several potassium channels that open and close during the action potential.^{4,12,13} For a normal function, the channels must open and close in a coordinated sequence. Inhibition, known as loss of function or activation (gain of function) of the channels, is linked to a greater risk of severe arrhythmias. The channels are identified by the gene encoding the channel, the alpha subunit (the pore or channel), and the current that carries it through.¹³

Immediately following the upstroke of the action potential (phase 0) due to rapid entry of sodium (*INa*), two small potassium currents are activated, the *Ito,f* (fast) and the *Ito,s* (slow) currents producing the notch in action potential.^{12, 13} The *KCND2* and *KCND3* genes encode for the alpha subunits *Kv4.2* and *Kv4.3* responsible for the rapid repolarizing current *Ito,f*.¹⁴ The *KCNA4* gene encodes for the channel *Kv1.4*, responsible for the transient outward of the slow repolarizing current, *Ito,s*.^{3,12} Quinidine exerts inhibitory actions on these channels prolonging repolarization.¹⁵

IKr is a rapid inward rectifier repolarizing current, that runs through phase 2 and the beginning of phase 3 of the action potential. This current moves through the alpha subunit pore *Kv11.1*. The *KCNH2/hERG* gene encodes the *Kv11.1* subunit.^{12,13} Inhibition of *IKr* delays the process of repolarization, which manifests with a long QTc interval on the ECG. The slow repolarization allows sufficient time for the inactive calcium channels to reactivate, leading to early calcium influx (early afterdepolarizations) that, if of sufficient magnitude, may trigger an arrhythmia.^{4,9} *Kv11.1*-channel inhibition or decreases in the number of mature functional channels is associated with long QTc.^{3,14,16} The effect of *IKr* inhibitors increases at low heart rates and low extracellular potassium concentrations. This explains the greater QTc prolongation and increased risk of TdP reported when hERG channel inhibitors are given in patients with bradycardia and/or hypokalemia.¹⁷

Drugs may directly inhibit the hERG channels and/or decrease the amount of functional, mature, channels in the plasma membrane, decreasing *IKr* currents.^{4,8,9} The number of mature channels is determined by the rates of synthesis, trafficking, and degradation of the channels. The half-life of the hERG channels is nearly 11 hours.¹⁸ The channels are glycosylated in the endoplasmic reticulum (core glycosylation) and the Golgi apparatus (full glycosylation), followed by insertion in the cell

Table 1. Effects on cardiac ion channels and pro-arrhythmic actions of drugs with purported or demonstrated efficacy in the treatment of COVID-19

Drug	Drug class	<i>In vitro</i> effects on ion channels/currents	Arrhythmia reports
Lopinavir, ritonavir, nelfinavir, saquinavir, atazanavir	Antivirals/protease inhibitors	Inhibition of KCNH2-hERG and <i>IKr</i> . Atazanavir also decreased hERG channel density	Long QTc or TdP, or both reported.
Remdesivir, fapinavir	Inhibitors of RNA polymerase	No evidence found. One case report. Dedicated QT studies are needed.	No reports
Chloroquine, OH-chloroquine	Anti-malarial	KCNJ2-Kir2.1- <i>IK1</i> , KCNH2-hERG-Kv11.1- <i>IKr</i> , At higher concentrations inhibits <i>INa</i> & <i>Ica</i> .	Reports of Long QT, T wave abnormalities, V Tach/TdP / cardiac arrest
Azithromycin	Antibiotic	KCNH2-hERG- <i>IKr</i>	Long QT, T wave abnormalities, V Tach/TdP
IL-6, TNF- α , Anti-Ro/SSA antibodies, nuclear factor- β	Cytokines/pro-inflammatory antibodies	IL-6 inhibits <i>IKr</i> currents, and decreases KCNH2- hERG channel mRNA and protein expression (via JAK pathway and/ or ROS production). TNF-α inhibits <i>IKr</i> currents and reduces the amount of membrane hERG channels. TNF- α also inhibits <i>Ito</i> currents and the amount of α -subunit Kv4.2 protein. Anti-Ro antibodies against antigen Ro52/TRIM21, inhibits KCNH2-hERG channels and <i>IKr</i> . NF- β inhibited <i>Ito,f</i> .	
Anakinra, canakinumab, rinolacet	Interfere with IL-1 actions	No data found	No reports
Sarilumab, siltuximab, tocilizumab	IL-6 antagonists	No evidence. May shorten long QT.	No reports
Axitinib, cabozantinib imatinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, vandetanib,	TKIs	Inhibit hERG/KCNH2 channels and <i>IKr</i> . Vandetanib also inhibits the <i>IKs</i> and <i>IK1</i> , <i>INa</i> and <i>Ica</i> , at higher concentrations. Sunitinib also inhibits <i>INa</i> currents at higher conc.	Long QTc and increased risk for TdP and SCD.
Ibrutinib	BTKI	Disrupted mitochondrial and ER calcium handling	Increases risk of A Fib, V tach, SV tach, HF, HT. Associated with short QT and delayed afterdepolarizations.
Baricitinib, ruxolutinib	JAKI	No evidence	No reports
Casirivimab + imdevimab bamlanivimab + ezetivimab.	Monoclonal antibodies	No evidence	No reports

Abbreviations: TKIs, tyrosine kinase inhibitors; BTKI, Bruton's tyrosine kinase inhibitors; JAKI, janus kinase inhibitors; TNF, tumor necrosis factor; IL-6, interleukin-1.

Currents are shown in bold italic font. *IKr*: rapid inward rectifying potassium current that develops through phases 2 and 3 of the AP, and is needed for membrane repolarization. *IKs*: slow inward rectifying potassium current that develops through phases 2 and 3 of the AP, and is needed for membrane repolarization. *IK1*: inwardly rectifying current that develops after the AP, and maintains the negative resting membrane potential during diastole. *Ito,f*: transient outward rapid repolarizing potassium current, involved on the notch of the AP. *INa*: rapid inward sodium current that determines the phase zero of the AP and membrane depolarization. *Ica*: voltage-dependent calcium current during the plateau of the AP, needed for contraction.

membrane. Channel degradation occurs by ubiquitination at the ER and subsequent proteasomal degradation. Caveolin-3 acts through the ubiquitin-ligase Nedd4-2 to regulate the amount of mature hERG channels, increasing ubiquitination and subsequent degradation.^{19,20} Besides, rififylin, the RING finger ubiquitin ligase, can participate in the process of hERG channel-ubiquitination.²¹

Mutations in the KCNH2-hERG gene may produce a mutated channel, which cannot be appropriately trafficked to the cell membrane. The reduced number of functional channels resultant from the gene mutation, clinically known as LQTS2, is characterized by the presence of ventricular arrhythmias and reports of SCD.²²

IKs is known as the slowly activating delayed rectifier

repolarizing current. This current moves through the channel-alpha subunit, Kv7.1, which, in turn, is encoded by the KCNQ1 gene. The *IKs* current plays a role in cardiac repolarization. Gene mutations can affect the function of the channel decreasing *IKs* current, delaying repolarization. Such mutation presents as the LQTS1. Drugs, although less frequently and often at doses higher than needed to inhibit *IKr*, may inhibit the *IKs* current.⁴

IK1 is an inwardly rectifying current that develops during diastole, keeping negative the resting membrane potential. Kir2.1. is the alpha-pore-forming subunit of the channel, which is encoded by the KCNJ2 gene. Bidirectional polymorphic ventricular tachycardia, associated with repolarization abnormalities (long QTc,

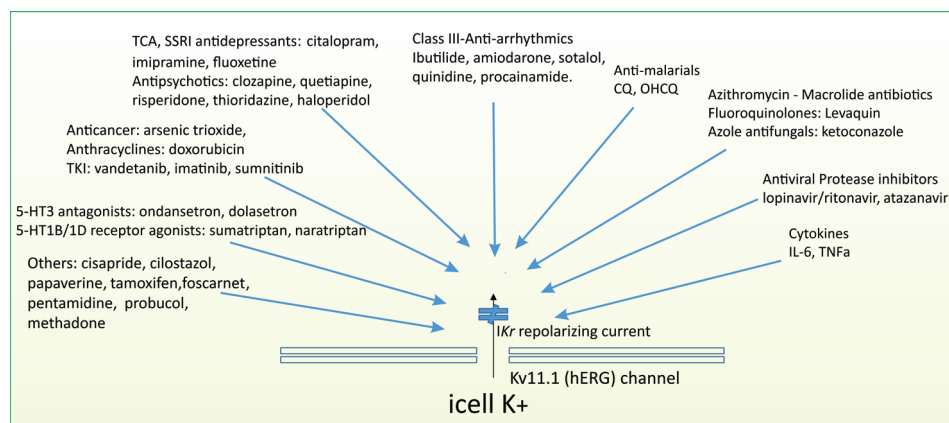


Fig. 1. The promiscuity of the hERG channels: Inhibitors of the hERG (Kv11.1) channels and *IKr* currents. The drugs depicted in the figure have been shown to inhibit cardiac hERG (Kv11.1) channels and the *IKr* current that moves through the channels. Some prototype drugs are provided. For further details, see references 8 and 9. Abbreviations: VEGFR: vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor; TCA: tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; IL-6, Interleukin-6; TNF α : tumor necrosis alpha; 5-HT: 5-hydroxytryptamine (serotonin).

large U waves, frequent PVCs), are reported in patients harboring loss of function mutations in the *KCNJ2* gene. Inhibition of *IK1* by hypokalemia and stimulation of beta-receptors inhibit *IK1* currents, increasing the risk of arrhythmias.^{23,24}

In summary, inhibition of *IKr*, *IKs*, *IK1*, and/or *Ito* currents interfere with membrane repolarization, lead to long QT, and favor the development of after-depolarization, thereby increasing the risk of triggering ventricular tachycardia, TdP, and SCD. Direct inhibition of hERG channels and reduced number of hERG channels (Kv11.1), are the commonest cause of drug-induced and congenital LQTS, respectively, and severe ventricular arrhythmias (Fig. 1).

Pro-arrhythmic potential of drugs used for the treatment of COVID-19 disease

Antivirals, long QT and risk of TdP and SCD

Protease inhibitors

Protease inhibitors, which inhibit viral protein synthesis, have been employed to treat patients with COVID-19.²⁴ By inhibiting 3-chymotrypsin-like protease, the combination of lopinavir and ritonavir has been shown to exert in vitro activity against novel coronaviruses.²⁵ Despite initial expectations, a recent randomized control trial on the use of lopinavir/ritonavir, failed to show survival benefits.²⁵

The use of protease inhibitors was associated with QTc prolongation, and/or TdP.²⁶ However, in HIV patients treated with protease inhibitors, the presence of long QTc was unrelated to drug use, and was related to the length of HIV infection and to the presence of known factors that lead to long QT.^{27,28} Further, in patients with severe COVID, the lopinavir-ritonavir combination did not induce QT prolongation or serious arrhythmic events.²⁹

Studies in HEK293 cells and cardiac myocytes showed that saquinavir, lopinavir, ritonavir, and nelfinavir have inhibitory actions on *IKr*.²⁶ Atazanavir inhibits hERG channels and *IKr* currents, likely by binding to the S6

channel-domain (residues Y652 and F656).³⁰ In addition, with longer times of exposure, atazanavir interferes with channel glycosylation, reduces the quantity of membrane hERG that is fully glycosylated. Such dual-action, channel inhibition, and reduced number of mature channels in the membrane may account for the potent inhibitory actions of atazanavir on *IKr* current.^{9,31} Besides, protease inhibitors can increase the levels of reactive oxygen species (ROS), which may exert inhibitory and stimulatory actions on several ion channels and transporters.³¹⁻³³ In cardiac myocytes, protease inhibitors induce depolarizing chloride outward currents due to increases in mitochondrial ROS, which may play a pro-arrhythmic role.³¹

In summary, more evidence suggests that protease inhibitors can inhibit the hERG channel, leading to long QT, and increase the risk of patients to TdP (Table 1). Monitoring the QT interval is recommended in patients with COVID-19 treated with protease inhibitors, in particular when combined with azithromycin, CQ, or OHCQ, or with any QT-prolonging drugs.²⁶

RNA polymerase Inhibitors

Remdesivir and Favipiravir inhibit viral RNA polymerase interfering with RNA Synthesis. Both drugs are broad-spectrum antivirals. Remdesivir is an adenosine nucleotide analog, RdRp inhibitor, and Favipiravir, a guanosine nucleotide analog, RdRp inhibitor.^{33, 34} In particular, remdesivir is employed for the treatment of COVID-19.^{25,34-36} In vitro studies demonstrated that remdesivir is a potent inhibitor of coronaviruses. Remdesivir inhibits SARS-CoV-2 with EC₅₀ and EC₉₀ values of 0.77 μ M and 1.76 μ M, respectively.^{37,38} Concentrations 5-10 times higher than remdesivir's EC₉₀ for COVID-19 are reached during the initial 200 mg IV infusion over 30 minutes.

No reports of QT prolongation, TdP, or cardiac arrhythmias were found for remdesivir and favipiravir (Table 1). A QTc study in Japanese adults found no effects of favipiravir.³⁹ Two cases of QTc prolongation were

reported, one during favipiravir therapy in one Ebolavirus-infected patient,⁴⁰ and another in one patient infected with COVID-19 during remdesivir therapy⁴¹; however, this patient was also treated with azithromycin. In summary, we found no studies other than these two case reports, to suggest that RNA polymerase inhibitors prolong the QTc interval, or that these drugs interfere with cardiac ion channels. Dedicated studies on the potential effects of remdesivir and favipiravir on the QT interval are needed.

Chloroquine and hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (OHCQ) have been used to treat COVID-19 infection.³⁷ OHCQ and CQ inhibit the synthesis of sialic acids, affecting protein glycosylation and disrupting SARS-CoV-2 attachment and entry into cells.^{37,38,42} Initially, these drugs were extensively used; however, recent evidence suggests that CQ and OHCQ are ineffective in the patients that are hospitalized with COVID-19. The US FDA revoked its authorization for emergency use to treat hospitalized patients with COVID-19.⁴³ SARS-CoV-2 entry into lung epithelial cells seems not to require low-pH processing in endosomes, which may account for the poor efficacy of CQ and OHCQ against COVID-19 disease in clinical trials.

The cardiovascular adverse events reported with CQ and OHCQ are TdP, long QT, hypotension, and ventricular tachycardia³⁷ (Table 1). Patients experiencing an overdose may present cardiovascular collapse, cardiac arrest, and hypokalemia. Cardiovascular side effects occurring less than 0.1%, include hypotension, cardiomyopathy, T wave inversion, or depression with QRS widening.⁴⁴

The effects of CQ and OHCQ on cardiac ion channels could account for the reported cardiac adverse events. CQ inhibits the *IK1* and the hERG channel *IKr* currents (Table 1). At higher and toxic concentrations, CQ can also block sodium and calcium channels. Contrary to most of the hERG blockers and ion-channels blockers that block the currents acting at the transmembrane site, CQ inhibits the potassium channel acting on the cytoplasmic side.⁴⁵ CQ binds to the acidic residues (Glu224, Glu299, Asp255, Asp259, and Phe 254) located in the cytoplasmic side of the channel pore.⁴⁵ Thus, the long QTc and TdP reported with these drugs likely result from inhibition of potassium currents.⁴⁶ HERG inhibition is not limited to CQ and OHCQ, since it is observed with most antimalarial drugs.^{3,47}

Azithromycin

Azithromycin, as well as other macrolide antibiotics, has been reported to induce long QTc and to increase the risk of ventricular arrhythmias due to inhibition of the hERG (Kv11.1) channel and the *IKr* current^{48,49} (Table 1). Besides, azithromycin increases the dispersion of repolarization, favoring the development of TdP.⁵⁰

Adverse event reports from 2004 to 2011 revealed a total

of 203 events, long QT-TdP (63 cases), and ventricular tachycardia or SCD (140 cases), likely leading to 65 deaths that were associated with azithromycin treatment.⁵¹ Prolongation of the QRS interval and complete heart block were also reported as adverse events.⁵² Retrospective, observational studies revealed that use of azithromycin, moxifloxacin, and levofloxacin was connected with an increase in the risk of cardiovascular events, including a ventricular arrhythmias.^{53,54} However, in a collection of 12 case reports of possible azithromycin-induced/associated QTc interval prolongation and TdP, there was no association between the duration of the QTc and the dose of azithromycin employed.⁵³ Moreover, causality was not proven, since all patients had additional risk factors for long QTc.⁵⁴ An increased risk in cardiovascular deaths associated with azithromycin use was reported in a retrospective study in young adults; however, the study design did not allow to determine whether the events were due to the azithromycin, the comorbid conditions associated with its use, or combination of both factors.⁵⁵

In summary, the increased risk in cardiovascular events and mortality reported with azithromycin use is greater in patients with multiple preexisting cardiovascular comorbidities, electrolyte abnormalities, and complex medication regimens. Consequently, a higher risk is expected when azithromycin is used in COVID-19 patients. These patients requiring close ECG monitoring, mainly in the presence of heart failure, ischemic heart disease, electrolyte abnormalities, and in those treated with anti-COVID-19 long QT drugs, such as CQ, OHCQ, protease inhibitors such as lopinavir/ritonavir, TKIs, and the Bruton's tyrosine kinase inhibitors (BTKI) (Table 1).

Combination of OHCQ, azithromycin, and protease inhibitors

A combination of long QT drugs should be avoided since it is associated with a greater risk of triggering TdP.⁴ In a randomized trial in subjects treated with OHCQ (1000 mg/qd), the addition of azithromycin prolonged the QTc interval in a dose-dependent manner, from 10 to 14 milliseconds.⁵⁶ Reports of long QT and/or ventricular tachycardia including TdP were more common with azithromycin monotherapy than with OHCQ monotherapy and increased with combination treatment.⁵⁷ The need for patient monitoring is known to prevent TdP. In a retrospective study of COVID-19 patients, Jain and co-authors⁵⁸ reported that close monitoring of QT and associated risk factors prevented the development of arrhythmic events. The authors analyzed over 2000 ECGs from 524 patients, most with COVID-19 infection. Patients who developed long QT were managed with electrolyte correction and by stopping nonessential long-QT drugs.

In COVID-19 patients, the use of OHCQ combined with either atazanavir or azithromycin required preventive discontinuation of OHCQ in nearly one-third of the

patients. None of their patients developed TdP. However, severe QT prolongation (QTc >500 ms) was seen in 11% of patients treated with OHCQ⁵¹ and in 9%⁵² of those treated with azithromycin drugs discontinuation was reported in 3.5% of the patients,⁵² and no TdP or arrhythmic deaths were reported.^{59,60}

In summary, studies in non-COVID-19 and COVID-19 patients ratify that both OH-QC, protease inhibitors, and azithromycin prolong the QT interval and that their combination produces greater QT lengthening, with the associated increased risk of developing TdP (Table 1). Close monitoring of these patients, discontinuation of nonessential drugs, and correction of electrolyte abnormalities is recommended and was successfully shown to prevent the development of severe ventricular arrhythmias.⁵⁸

Inflammation and long QT: IL-1 and IL-6 antagonists

COVID-19 hyperinflammatory syndrome

COVID-19 severity and outcomes seem to be determined by the patient's immune-inflammatory response. Exaggerated production of ILs and tumor necrosis factor α (TNF- α) are involved in the multisystem inflammatory syndrome reported in COVID-19 patients with severe disease.³ Increased levels of inflammatory cytokines, ferritin, and D-dimer, associated with lymphocytopenia and thrombocytopenia, are present in these patients.³ Severely affected COVID-19 patients may present features suggestive of the cytokine storm syndrome, and occasionally features of the macrophage activation and secondary hemophagocytic-lymphohistiocytosis syndromes.^{3,61-63} These conditions are characterized by very high levels of interleukins, interferons, and of TNF- α .⁶² These pathophysiological considerations account for the ongoing clinical trials testing the use of IL-6 and IL-1 antagonists, and of drugs that interfere with JAK kinases in the management of COVID-19 patients with severe disease.⁶¹⁻⁶³

Long QT in inflammatory syndromes: Effects of interleukin antagonists

Cardiac muscle and conduction system abnormalities are described in animal models of Kawasaki disease. Mice injected with *Lactobacillus casei* cell-wall extract developed tachycardia and decreased R-wave amplitude, prolonged ventricular repolarization, and increased neural remodeling of the myocardium. Treatment with IL-1 signaling inhibitor, anakinra, for four days, corrected the ECG abnormalities and prevented the ventricular remodeling.^{64,65}

Patients with rheumatoid arthritis (RA) and chronic systemic inflammation often present with long QTc.⁶⁶⁻⁶⁸ The lengthening of the QTc interval and development of TdP were positively related to the circulating levels of IL6, IL1 β , TNF α and C-reactive protein (CRP).^{68,69,70} At pretreatment, nearly three-fourth of the RA patients showed QTc prolongation (452.3 ± 35.8 ms). In these

patients, tocilizumab (anti-IL-6 therapy) shortened the QTc interval to 428.1 ± 34.3 milliseconds, with all patients having QTc intervals shorter than 440 milliseconds. Shortening the QT interval was related to lowering in the TNF α and CRP levels.⁷¹ Of interest, nearly 10% of patients with SLE had longer QTc than healthy controls, and around 3% of the SLE patients showed marked QTc prolongation (>500 ms). The QTc prolongation was directly associated with inflammatory markers and disease activity.^{69,70} Notably, in these patients, anti-IL-6 therapy with tocilizumab resulted in QTc shortening.⁷²

Cytokines and cardiac channels

The effects of cytokines on cardiac ion channels support the above-described observations of long QT in RA and SLE patients (Table 1). In HEK transfected cells with hERG channels, and ventricular myocytes, IL-6 inhibited *IKr* currents, decreased KCNH2- hERG channel mRNA and protein expression, and prolonged the duration of the ventricular action potential.⁷³ IL-6 receptors and the Janus kinase (JAK) pathways mediated the inhibition of hERG induced by IL-6. Besides the JAK pathway, increases in ROS and ceramide signaling pathways may also mediate the effects of the cytokines on the ionic currents and prolongation of the QTc interval.

TNF- α was also shown to inhibit *IKr* currents in HEK293 cells and ventricular myocytes⁷³ and to decrease the amount of mature hERG channels on the cell membrane.^{74,75} In addition, in rat ventricular myocytes, TNF- α inhibited *Ito* currents and the amount of Kv4.2 in the cell membrane,⁷⁶ and nuclear factor- β decreased *Ito,f* acting on KChIP2 expression.⁷⁷ Besides the cytokines, anti-Ro antibodies (against antigen Ro52/TRIM21), obtained from patients with autoimmune disease, inhibited *IKr* current acting on KCNH2-hERG channels.^{78,79} Anti-Ro/SSA antibodies, of the 52kD subtype, seem to be responsible for an immune-mediated LQTS, acting the hERG-Kv11-1 channel pore⁸⁰ (Table 1).

In summary, *in vitro* studies on ion channels and clinical observations in patients with inflammatory syndromes suggest that the long QTc and the increased risk of arrhythmia observed is associated with high levels of cytokines. These effects are more likely due to the inhibition of hERG function and channel synthesis, and the interference with *Ito* currents. Consequently, it is not surprising that anti-cytokine therapies may shorten the QTc interval.^{71,72} We found no reports of QT prolongation or TdP associated with the use of the anakinra, an antagonist of IL1 receptors, with rinolcept, a soluble decoy receptor, canakinumab, a monoclonal anti-IL-1 β antibody, and for the human monoclonal antibodies against IL-6 receptor, tocilizumab, sarilumab, and siltuximab (Table 1).

Tyrosine kinase inhibitors

Tyrosine kinases stimulate the phosphorylation of proteins transferring phosphate groups to their tyrosine residues, regulating cell growth, migration, differentiation, and

death; effects that are responsible for the use of TKI in different malignancies. Some of the TKIs exert *in vitro* inhibitory activity against SARS-CoV-2.⁸¹ An additional important aspect is the use of TKI in cancer patients infected with COVID-19.

Cardiac toxicity has been reported in patients treated with TKI.^{3,81,82} Treatment with VEGFR-TKIs (sunitinib, axitinib, vandetanib, sorafenib, pazopanib, cabozantinib, ponatinib, and regorafenib) was associated with a four-time greater risk for QTc prolongation⁸³⁻⁸⁵ (Table 1). Due to the increased risk of arrhythmia and SCD, vandetanib use is restricted *via* a Risk Evaluations and Mitigation Strategy program.⁸² Vandetanib must not be given combined with other long QT drugs. One-third of cancer patients treated within imatinib, nilotinib, or dasatinib developed QT prolongation during drug administration. QTc intervals longer than 500 milliseconds were found in 53 administrations, ventricular tachycardia in nine, TdP in two, and SCD in three administrations.⁸⁴

Vandetanib inhibits hERG/KCNH2 channels decreasing *IKr* current amplitude, leading to a long QT. At higher concentrations, it inhibits the *IKs* and *IK1* potassium currents, interfering with *INa* and *ICa* currents at high micromolar concentrations.⁸⁶ Similarly, sunitinib was shown to inhibit *IKr* currents at low micromolar and *INa* currents at higher micromolar concentrations.⁸⁷ Imatinib mesylate inhibited *IKr* in HEK-293 cells and *Xenopus* oocytes⁸⁸ (Table 1).

In summary, TKI preferentially inhibits the hERG-Kv11.1 channels and the corresponding *IKr* currents, and interferes with other potassium, sodium, and calcium currents at higher concentrations. Treatment with TKI is reported associated with long QTc and increased risk of TdP and SCD. Caution should be exerted and monitoring should be implemented during TKI administration. The combination of TKI with other long QT drugs should be avoided, and patients with comorbidities and electrolyte disturbances associated with long QT should be carefully monitored.

Bruton's tyrosine kinase inhibitors

BTK is a member of the Tec family of non-receptor tyrosine kinases. BTKs are involved in the B-cell signaling pathways involved in the growth and maturation of the B-cells. Inhibition of B-cell function may theoretically reduce the hyper-inflammatory immune response observed in severely ill patients with COVID-19.

Ibrutinib is being studied in hospitalized patients with COVID-19.^{89,90} Ibrutinib is the first human BTK inhibitor approved by the FDA.⁹¹ However, an increased risk of atrial and ventricular arrhythmias, sinoatrial arrest, heart failure, hypertension, and SCD was reported with ibrutinib.^{3,92-94} In patients with leukemia, atrial fibrillation was the most common cause of treatment discontinuation.^{95,96} A 4-9 fold increase in the incidence of atrial fibrillation was reported with ibrutinib.⁹⁷ Noteworthy, the increased

incidence of ventricular arrhythmias seemed not associated with QT prolongation.⁹⁸ In fact, episodes of polymorphic ventricular tachycardia occurred with a normal QTc interval, and with a short-coupled variant before the arrhythmia.⁹⁴ Besides, QT shortening has been described with ibrutinib.⁹⁵ It was proposed that this type of ventricular tachycardia is the consequence of disrupted calcium handling in the myocardium, favoring delayed afterdepolarization⁹⁹ (Table 1). Further studies are required to determine the mechanism of the pro-arrhythmic action of ibrutinib.

In summary, ibrutinib use is associated with an increased number of cardiac arrhythmias, such as atrial fibrillation, ventricular and supraventricular arrhythmias, and with a greater risk of heart failure and hypertension. Current evidence suggests that the ventricular polymorphic arrhythmias reported with ibrutinib occur in the absence of a long QT, but rather with either a normal or a short QT interval. Patients on ibrutinib therapy must be carefully monitored.

Janus kinase inhibitors (JAKI)

Baricitinib and ruxolitinib are selective inhibitors of the JAK1 and JAK2 enzymes, inhibiting the JAK-STAT signaling pathway. Its main clinical use is in the treatment of adult patients with moderately to severely active RA.⁹⁹ Besides its anti-cytokine activity, baricitinib may exert antiviral effects. Baricitinib has an affinity for AP2-associated protein AAK1, interfering with the endocytosis of SARS-CoV-2.¹⁰⁰ In an open pilot study conducted in hospitalized with moderate pneumonia due to COVID-19 pneumonia, baricitinib combined with lopinavir/ritonavir improved clinical and laboratory parameters, no patient required ICU support, and most patients were discharged in good health.¹⁰¹ Besides, in hospitalized patients with COVID-19, baricitinib in combination with remdesivir was more effective than remdesivir alone in reducing the time to recover from COVID-19 infection.¹⁰²

Baricitinib inhibits hERG channels at high concentrations. Its IC_{50} is in the range of 50 to 60 μ g/mL. Steady-state levels obtained with an 8 mg daily dose were 1000 times lower than those required to inhibit hERG.¹⁰³ No significant QTc prolongation was reported with a single dose of 40 mg.¹⁰³ We found no published reports suggestive of baricitinib-induced QT prolongation, of its effects on potassium channels and cardiac ion channels. In summary, although more studies are needed, baricitinib appears to have a low potential for inducing long QT and associated TdP (Table 1).

Monoclonal antibodies: casirivimab-imdevimab and bamlanivimab-etesevimab

Casirivimab (REGN10933) and imdevimab (REGN10987) are two human monoclonal antibodies. These antibodies were constructed to bind to two different areas of the spike protein of SARS-CoV-2, and are expected to inhibit virus'

binding and entry into cells. When employed in patients with COVID-19 and at high risk for severe disease, the antibody combination reduced the viral load (less virus penetrates the cells, reducing viral replication and infectivity) and the number of hospitalizations and visits to the ED.¹⁰⁴ Bamlanivimab (LY-CoV555) either alone or preferably in combination with etesevimab, are also neutralizing human monoclonal IgG1 antibodies, which to the receptor-binding domain of the spike protein of COVID-19.

The FDA has granted the EUA for the use of the monoclonal antibodies as a single IV administration, in non-hospitalized patients with mild to moderate COVID-19, at high risk for progressing to severe COVID-19, and as post-exposure prophylaxis.¹⁰⁵ The latter was defined as been 65 or older, and/or with chronic medical conditions. We found no reports of QT prolongation, ventricular tachycardia, or TdP during or following administration of these monoclonal antibodies (Table 1). Additional studies are needed to draw firm conclusions about any adverse cardiac toxicity.

Concluding Remarks

It is of pharmacological and clinical significance the observed lack of apparent selectivity to inhibition of the hERG channels by a large number of structurally different pharmacological agents. Most of the drugs that inhibit hERG channels seem to act at the channel pore tetramer. Channel opening during membrane depolarization seems required for the binding of most channel inhibitors (Table 1, Fig. 1). Therefore, it was not unexpected that several of the drugs with purported anti-COVID-19 activity would inhibit the hERG channels, increasing the risk of cardiac arrhythmias. Furthermore, some of these agents, particularly at higher doses, may also interfere with other potassium (*IK1*, *IKs*, *Ito*) currents, as well as with sodium (*INa*), and even calcium (*ICa*) currents, increasing their cardiac toxicity. Further studies on the molecular and electrical gating mechanism modulating hERG gating mechanisms are required to further understand the mechanism of hERG channel promiscuity.

Inhibition of the rapid depolarizing *IKr* current prolongs the repolarization time, which manifests with a long QTc interval on the ECG. In high-risk patients, prolonged repolarization facilitates the development of early afterdepolarizations, which may induce a ventricular arrhythmia that may be severe and even fatal. Antiretroviral drugs, azithromycin, CQ and OHCQ, and some of the TKIs inhibit the *IKr* current. Inhibition of *IKr* is achieved by direct drug action on the hERG channel, and/or by a reduced amount of channels in the cell membrane. Decreased synthesis, faulty channel trafficking, and glycosylation, and/or increased degradation can reduce the number of mature membrane channels. Of interest, Ibrutinib, a BTKI, increases the risk of atrial fibrillation, and ventricular tachycardia not associated with long QTc,

Review Highlights

What is the current knowledge?

- √ The severe acute respiratory syndrome, named COVID-19, is caused by CoV-2, and is characterized by high infectiveness, morbidity, and mortality.
- √ The lack of an effective cure led to compassionate and emergency use approval of therapies with insufficient efficacy and safety data.
- √ Arrhythmic events are more frequent in severely ill, hospitalized, COVID-19 patients.
- √ Drug-induced inhibition of hERG potassium channels is the most common cause of long QT, and TdP.

What is new here?

- √ The following drugs with proposed anti-COVID-19 activity inhibit hERG channels and increase the risk of TdP: azithromycin, OHCQ, CQ, lopinavir/ritonavir/atazanavir, TKI (i.e., vandetanib). The BTKI, Ibrutinib, increases the risk of atrial fibrillation and ventricular arrhythmias. The mechanisms of channel inhibition are discussed.
- √ In addition to the above-mentioned drugs, endogenous cytokines, IL-6 and TNF- α can inhibit hERG channels interfering with potassium currents. When associated with pro-arrhythmic drugs, high levels of cytokines observed in severe COVID-19 can further increase the risk of severe arrhythmias.
- √ No evidence of pro-arrhythmic activity was found for remdesivir, dexamethasone, baricitinib, and human monoclonal antibodies (bamlanivimab + etesevimab, and casirivimab + imdevimab).
- √ In addition to drugs with pro-arrhythmic activity, patients' old age, cardiac comorbidities, and extensive inflammation can explain the increased arrhythmic events reported in patients with severe COVID-19 disease.

but rather with a short QTc. In addition to the above-mentioned drugs, the cytokine storm-hyper-inflammatory response, described in severe COVID-19 infection, favors arrhythmogenesis. High concentrations of inflammatory cytokines, IL-6, TNF- α , and nuclear factor β can inhibit the *IKr* and the *Ito* currents, which are essential for normal repolarization, and may account for the 6-fold greater incidence of arrhythmias reported in the more severely ill COVID-19 patients.

In summary, besides drug therapy, older age, presence of high-risk comorbidities, excessive immune-inflammation, and severe COVID-19 disease can additively inhibit cardiac ion channels, increasing the risk for ventricular arrhythmias. Avoiding therapies with a high risk/benefit ratio for arrhythmogenesis, strict patient EKG monitoring for QT changes, maintaining K⁺ and Mg⁺⁺ concentration within normal range, avoiding long-QT drug combination, and use of effective anti-inflammatory therapies to lower cytokine levels (dexamethasone) are the mainstay for the prevention of triggered arrhythmias in COVID-19 patients.

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Ethical statement

Not applicable.

Competing interests

There are no competing interests.

Authors' contribution

DdLR contributed to the bibliographic search, bibliographic organization, and writing of the manuscript. MA contributed to the safety evaluation of anti-COVID-19 drugs. LXC initiated and organized the study, conducted the data analysis, and contributed to the writing and reviewing of the manuscript.

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