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Off-label use of chloroquine, hydroxychloroquine, azithromycin and lopinavir/ritonavir in COVID-19 risks prolonging the QT interval by targeting the hERG channel

Zheng Zequn [a], Wu Yujia [a], Qian Dingding [b], Lian Jiangfang [b,*]

[a] Medical College, Ningbo University, Ningbo, Zhejiang, 315000, China
[b] Department of Cardiovascular, Lihuili Hospital Affiliated to Ningbo University, Ningbo, Zhejiang, 315211, China

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ABSTRACT

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses an enormous challenge to the medical system, especially the lack of safe and effective COVID-19 treatment methods, forcing people to look for drugs that may have therapeutic effects as soon as possible. Some old drugs have shown clinical benefits after a few small clinical trials that attracted great attention. Clinically, however, many drugs, including those currently used in COVID-19, such as chloroquine, hydroxy-chloroquine, azithromycin, and lopinavir/ritonavir, may cause cardiotoxicity by acting on cardiac potassium channels, especially hERG channel through their off-target effects. The blocking of the hERG channel prolongs QT intervals on electrocardiograms; thus, it might induce severe ventricular arrhythmias and even sudden cardiac death. Therefore, while focusing on the efficacy of COVID-19 drugs, the fact that they block hERG channels to cause arrhythmias cannot be ignored. To develop safer and more effective drugs, it is necessary to understand the interactions between drugs and the hERG channel and the molecular mechanism behind this high affinity. In this review, we focus on the biochemical and molecular mechanistic aspects of drug-related blockade of the hERG channel to provide insights into QT prolongation caused by off-label use of related drugs in COVID-19, and hope to weigh the risks and benefits when using these drugs.

1. Introduction

By the end of October 2020, in the nearly one year since the end of 2019, coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread throughout the world, with more than 46 million infections and over 1.1 million deaths, making it a terrifying destroyer of human life recently. Effective and safe treatments are urgently required in the COVID-19 pandemic, with scientists striving for rapid research and application of drugs, and at least 12 potential COVID-19 treatments are now being tested. This research is a race against COVID-19 (Kupferschmidt and Cohen, 2020). However, although a series of drugs approved for other indications and a variety of research drugs are being studied in hundreds of clinical trials (available at ClinicalTrials.gov) around the world, there is currently no Food and Drug Administration (FDA)-approved COVID-19 drug (Jan et al., 2020; Panel, 2020). In the treatment guidelines issued on April 21, the National Institutes of Health (NIH) pointed out that, at present, there are no drugs proven to be safe and effective in the treatment of COVID-19 (Panel, 2020).

Early on in the pandemic, after small clinical randomized trials, some compounds were shown to be beneficial to patients, such as antimalarial drugs (Mercuro et al., 2020; Saleh et al., 2020; Wang et al., 2020; Yao et al., 2020) and antiviral drugs (Cao et al., 2020a; Hung et al., 2020). However, the evidence of effective treatment with the use of these drugs is still insufficient, and the advocation of some of these drugs, such as chloroquine (CQ), by some public figures may hinder research on new potential therapeutic drugs (Ledford, 2020). More recently, a large-scale multicenter clinical randomized controlled trial (RCT) conducted in the UK has been shown that the 28-day mortality rates of hospitalized patients with COVID-19 in the hydroxychloroquine (HCQ) treatment group were higher than those in the usual-care group (59.6% vs. 62.9%) (Horby et al., 2020). This result reminds us to reconsider a question: Is it appropriate to use any drug on COVID-19 patients before large-scale RCTs are completed? In addition, a noticeable problem is that these

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drugs may increase the risk of QT prolongation and ventricular arrhythmias (Giudicessi et al., 2020; Naksuk et al., 2020). A statement from the Canadian Cardiovascular Society (CCS) recommended that the use of unnecessary drugs be discontinued, especially CQ, HCQ, azithromycin, and lopinavir/ritonavir, and baseline electrocardiograms (ECGs) should be performed in high-risk patients (Sapp et al., 2020). Indeed, the use of the drugs mentioned above alone or in combination against COVID-19 has a risk of prolonging the QT interval, and even CQ and HCQ have been listed as drugs that can cause direct myocardial toxicity. More importantly, patients with potential congenital arrhythmias, particularly long QT syndrome (LQTS), are at greater risk of fatal arrhythmias such as Torsades de Pointes (TdP) while receiving the above drugs at present (Giudicessi et al., 2020; Kannankeril et al., 2010).

It is well known that many factors participate in prolonging the QT interval, and these factors are mainly divided into congenital LQTS (cLQTS), caused by genetic mutation, and acquired LQTS (aLQTS), mainly caused by off-target drug effects (also called drug-induced LQTS (diLQTS)), which can both cause TdP (Cubeddu, 2016; Schwartz and Woosley, 2016). Importantly, the hERG (Kv11.1) channel is the main target of drugs in diLQTS (Kannankeril et al., 2010; van Noord et al., 2010). Many drugs, including antibiotics, antivirals, antifungals, antimalarials, and antidepressants, have been withdrawn from the clinic because of their severe potential arrhythmia targeting the hERG channel (Cubeddu, 2016; Mladěnka et al., 2018). The potential for hERG channel involvement in drug-associated arrhythmia is so strong that we need to pay more attention to the biological characteristics of the hERG channel itself to explain and understand the high affinity of drugs for COVID-19 for the hERG channel (Butler et al., 2019). An understanding of the molecular basis for hERG channel interactions with drugs is required to produce safer drugs for the treatment of diseases such as COVID-19.

2. The hERG channel

2.1. The significance of the hERG channel

The hERG channel is also known as the Kv11.1 channel or ERG1 potassium channel. The hERG gene encodes the pore-forming alpha subunit of a fast component of the delayed rectifier potassium channel (I_{Kr}), which plays a fundamental role in the three-phase repolarization of the ventricular action potential, i.e., the repolarization of cardiac myocytes (Vandenberg et al., 2012). hERG channel dysfunction contributes to a partial or complete red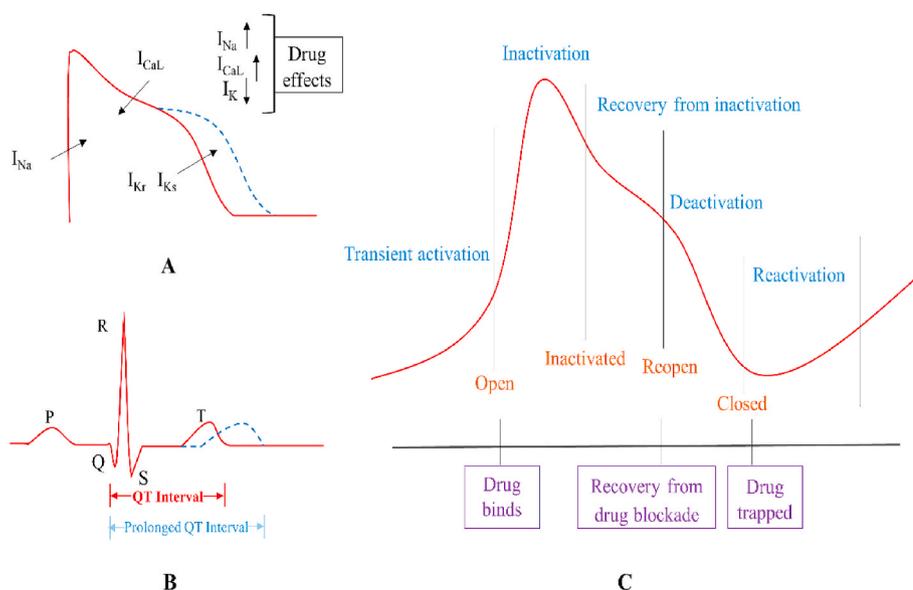uction in the I_{Kr} current, resulting in prolonged action potential duration (APD) (Smith et al., 2016), manifested as a prolonged QT interval on an ECG (Fig. 1B), and if the extension exceeds the normal range (440 ms in men, 460 ms in women), LQTS results (Schwartz and Ackerman, 2013; van Noord et al., 2010). Clinically, LQTS caused by hERG deficiency is called type 2 LQTS (LQT2), which is the second most common subtype of LQTS (Kapplinger et al., 2009).

The electrical activity of the heart is mediated by the regulation of the channels in which ions flow into and out of cardiomyocytes. Theoretically, ion currents that constitute the ventricular action potential include inward and outward currents, and the balance of outward and inward currents is the key to the formation of normal APD. Na^+ and L-type Ca^{2+} currents (I_{Na} and I_{CaL}, respectively) are the most important inward currents in cardiomyocytes, and the K^+ current (I_K) is the major outward current. Increased inward current or a weakening of outward currents due to drug effects can result in a prolongation of APD, leading to a prolonged QT interval (Fig. 1A) (van Noord et al., 2010). Excessive prolongation can facilitate the production of early after depolarization (EAD) in three-phase repolarization that will trigger TdP and even ventricular fibrillation if EAD reaches its threshold (Albert and Schuller, 2014).

A decrease in outward potassium currents causes a longer repolarization time due to the blocking of the hERG channel, the effect of which is consistent with strengthening sodium or calcium currents. Therefore, the effect of drug inhibition on the hERG channel appears to be corrected by drugs that block I_{Na} and I_{CaL}. A classic example is amiodarone, a widely used class III antiarrhythmic drug that inhibits multiple ion channels to balance the blocking of I_{Kr}; therefore, amiodarone leads to rare malignant arrhythmic events generated by potassium channel blockage. However, cardiac and non-cardiac QT-prolonging drugs often easily target the hERG channel but do not involve in other ion channels to cause arrhythmias. Thus, drugs against COVID-19 with single-ion-channel effects that act on the hERG channel are inevitably potentially arrhythmogenic. Many studies have focused on revealing the biological characteristics of hERG channels to explain possible mechanisms of drug action that involve various drug effects not only on the structure but also on the gating kinetics of these channels.

2.2. hERG channel structure and gating kinetics

The hERG channel shares structural homology with other voltage-gated potassium channels (Whicher and MacKinnon, 2016). The hERG

Fig. 1. A prolonged action potential duration (APD) by increased inward current and weakened outward currents induced by drugs (**A**) and manifested on an electrocardiogram (ECG) (**B**). The hERG channel undergoes a transient activation process of channel opening, followed by rapid inactivation and then recovery from inactivation. At this time, the channel opens again, followed by a slow deactivation process to close the channel. The opening of the channel is necessary for drug binding, and when the channel is closed, the drug is trapped due to the blocking effect and is released when the channel reopens (**C**).

channel is a tetramer, and four hERG subunits are arranged in a ring-shaped manner rather linearly arranged on the membrane (Vandenberg et al., 2012). Each subunit has six transmembrane fragments (S1–S6), an N-terminal Per-Arnt-Sim (PAS) domain, and a C-terminal cyclic nucleotide-binding domain (cNBD) (Barros et al., 2020; Shi et al., 2020; Warmke and Ganetzky, 1994). S1–S4 function as a voltage-sensing domain (VSD), and S5–S6 coupled with the intermediate pore loops of the four subunits constitutes the ion permeation pore-gate domain (PD) (Fig. 2A) (Barros et al., 2020; Wang et al., 2011). Recently, a new hERG channel structure obtained from cryo-electron microscopy (cryo-EM), named hERG$_T$, was discovered, with deletions in most of the expected unstructured cytoplasmic regions (Δ141–350 at the N-terminus and Δ871–1005 at the C-terminus) for preventing structural aggregation (Fig. 2A) (Wang and MacKinnon, 2017). hERG$_T$, with a resolution of up to 3.8 Å, retains gating properties similar to those of full-length channels because it does not change the major function of the hERG channel already recognized. hERG$_T$ provides new insights into the molecular basis of hERG channel blockade by high-affinity drugs, the binding of hERG channel activators, and unique hERG channel gating kinetics by demonstrating the importance of the special structure of hERG channels for the binding of compounds (Butler et al., 2019; Vandenberg et al., 2017).

The blockade of the hERG channel by drugs is associated with hERG channel conformational change. In the early stage of the action potential, the hERG channel slowly opens but rapidly inactivates. As the depolarization voltage continues to decrease, the hERG channel gradually recovers from the inactivation (Witchel et al., 2001). Due to recovery from inactivation, hERG currents improve during repolarization followed by a much slower deactivation (Barros et al., 2012; Vandenberg et al., 2017). The altering rate of inactivation and deactivation reflects the potential potency of drug blockade. Similarly, drugs show different affinities for the channel in its different conformational states (Fig. 1C). More recently, a selectivity filter at the hERG channel was reported as a pharmacological master mechanism to open potassium channels, offering a substantial boost in the design of channel activators to treat aLQTS or diLQTS (Schewe et al., 2019).

3. The pharmacology of the hERG channel

I_{Kr} is the target of class III antiarrhythmic drugs, such as dofetilide, amiodarone, and D-sotalol. These drugs and non-cardiac drugs, such as those for COVID-19, produce voltage- and dose-dependent hERG channel blockade due to direct blocking of ion pathways once the drugs enter cells (van Noord et al., 2010; Wang and MacKinnon, 2017). In addition to the direct blocking effect, the disruption of the biogenesis of the hERG channel is also a significant reason for the decrease in the I_{Kr} current (Fig. 3).

3.1. Structural basis of drug binding

Many studies have reported the importance of multiple aromatic residues for drug blockade based on differences in the homology among Kv channels via the mutagenesis of individual residues in the S6 helix (Han et al., 2011, 2015; Jie et al., 2017; Rajamani et al., 2006; Sánchez-Chapula et al., 2003; Sánchez-Chapula et al., 2002; Takemasa et al., 2008). Among them, two aromatic residues of S6, Tyr652 and Phe 656, are particularly significant (Fig. 2C). Mutations at these residues can attenuate the drug blocking effect, confirming their high affinity for drug binding. For example, when used in the treatment of COVID-19, CQ-generated channel blockade can be restored by mutation at Tyr652, showing that these key sites participate in channel blockade (Sánchez-Chapula et al., 2002). It is believed that the Y652A and F656A mutations decrease the inhibitory effect by 17 times and 75 times, respectively (Helliwell et al., 2018). In addition to the two key residues above, other residues at the bottom of the pore helix (e.g., Thr623, Ser 624, Val 625 and Phe 557 in the S5 helix) also contribute to drug binding equally as potently as Y652 (Mitcheson et al., 2000; Saxena et al., 2016).

The structure of hERG$_T$ retains all the functions essential for drug binding, which illustrates why these special amino acids of drug binding are so important (Wang and MacKinnon, 2017). The positions of these amino acids in the sequence and the molecular structure are highlighted, and they are arranged on the surface of elongated, relatively hydrophobic pouches protruding from the central cavity (Fig. 2B) (Wang and MacKinnon, 2017). These pockets provide potential interaction sites for hERG blockers (Butler et al., 2019). Furthermore, the narrow cavity leads to a more negative electrostatic potential, making it easy for positively charged drugs to bind (Wang and MacKinnon, 2017). To elucidate the chemical basis of drug binding, higher resolution structures will be needed in combination with molecular dynamics simulations. These simulations could accurately identify where and how drugs bind to the hERG channel and why they bind differently to distinct conformational states of the channel.
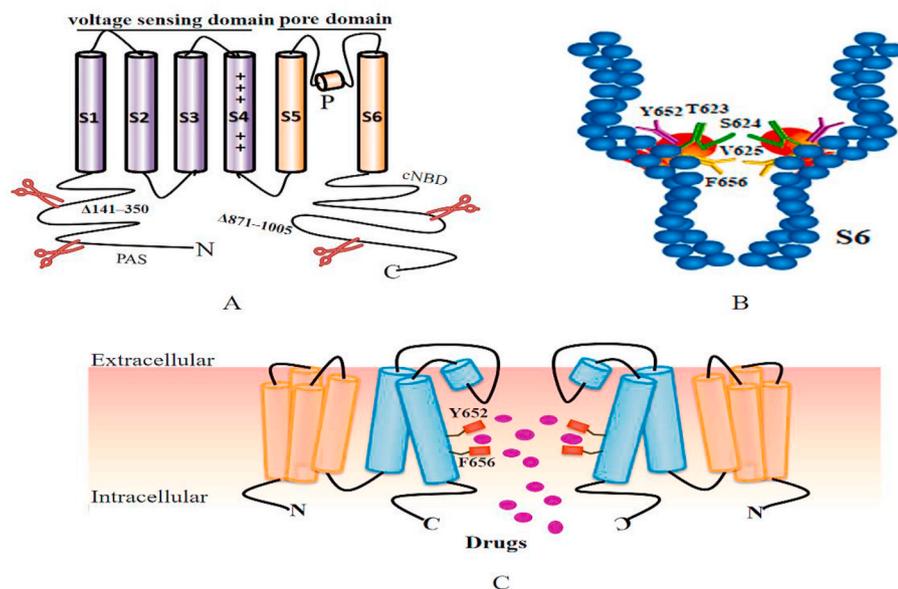
Fig. 2. hERG$_T$ structure and key drug-binding sites. The cryo-EM structure of hERG$_T$ (i.e., the hERG channel with deletions in cytoplasmic regions 141–350 at the N-terminus and 871–1005 at the C-terminus) (**A**). The positions of key amino acids of drug-binding sites in S6 obtained from hERG$_T$ are highlighted and arranged on the surface of hydrophobic pouches protruding from the central cavity (**B**). Four hERG channel subunits are coupled on the cell membrane to form a pore region (only two are shown) where the drug enters when the channel opens and binds to key drug-binding residues, including Y652 and F656 (**C**).

Fig. 3. Mechanisms of COVID-19 drugs blocking the hERG channel in cells. After COVID-19 drugs enter a cell, in addition to producing direct channel-blocking effect, they also interfere with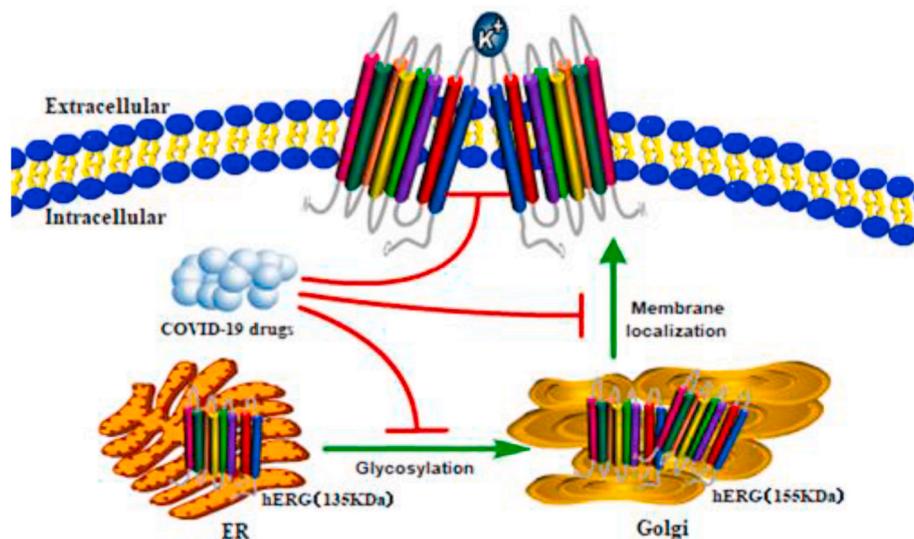 the glycosylation process (135 kDa–155 kDa), which affects channel maturation from the endoplasmic reticulum (ER) to the Golgi and thus hinders the membrane localization of mature proteins.

3.2. The disruption of hERG channel trafficking

As indicated earlier, drugs binding to the pore region of the hERG channel exert a direct blocking effect that disrupts the conduction of ions through the pore. Many different-structured drug groups targeting the hERG channel cause QT prolongation by disrupting the trafficking of protein (Dennis et al., 2007; Kuryshev et al., 2005; Nogawa and Kawai, 2014). These drugs include arsenic (Ficker et al., 2004), pentamidine (Kuryshev et al., 2005), fluconazole (Han et al., 2011) ketoconazole (Takemasa et al., 2008), fluoxetine (Hancox and Mitcheson, 2006), cardiac glycosides (Wang et al., 2007), rosuvastatin (Feng et al., 2019), thioridazine (Liu et al., 2020) and so on. Arsenic trioxide (As_2O_3) is the first example of a drug that produces hERG channel liability through the inhibition of channel protein trafficking by disrupting hERG-chaperone complexes to reveal a new significant mechanism in decreased I_{Kr} current (Ficker et al., 2004). Up to 40% of all hERG channel blockers exert combined hERG channel blockade and trafficking inhibition (Dennis et al., 2011). As an increasing number of drugs target the hERG channel, more drug studies have confirmed that the above two mechanisms can work together and are probably mediated by different mechanisms (Han et al., 2011; Hancox and Mitcheson, 2006; Rajamani et al., 2006; Takemasa et al., 2008), making the interfering effect on the hERG channel more complicated.

In general, numerous drugs reduce the generation of the mature form of the hERG channel (155 kDa) by disrupting the forward trafficking of the hERG protein from the endoplasmic reticulum (ER) to the Golgi (Fig. 3). This process is associated with molecular chaperones that help in protein folding and assembly. For instance, the inhibition of the chaperone protein Hsp 90 prevents maturation and promotes the proteasome degradation of hERG protein, thereby reducing the number of mature channels that can be integrated into the cell membrane (Cubeddu, 2016). Different maturation of the hERG channel protein can be estimated by comparing the expression levels of the two forms of this protein using Western blot. There is currently no definitive, relevant evidence to support the use of drugs that interfere with the maturation of the hERG protein in the treatment of COVID-19. The safe application of these drugs may require detailed information about blocking the intracellular mechanisms of the hERG protein.

3.3. Other mechanisms

Another issue worth considering is that many drugs may alter drug metabolism, which may further increase the plasma levels of drugs that extend the QT interval. Pharmacokinetic interactions usually involve agents metabolized by cytochrome P450 enzymes (van Noord et al., 2010). P450 (CYP) 3 A is the subfamily with the highest expression and includes the isoforms CYP3A4, CYP3A5, CYP3A7, and CYP3A43 (Eichelbaum and Burk, 2001). CYP3A4 is the isoform expressed in the liver and intestine (Eichelbaum and Burk, 2001), and it can oxidize a variety of drugs through many metabolic processes for detoxification (Dresser et al., 2000), and CYP3A4 is responsible for approximately 60% of the metabolism of currently known drugs (Feng et al., 2018; Zhou et al., 2005). Clinically important CYP3A4 inhibitors include antifungals (e.g., itraconazole and ketoconazole), macrolides (e.g., clarithromycin and erythromycin), antihypertensives (e.g., dihydralazine, verapamil, and diltiazem), and anti-HIV drugs (e.g., ritonavir and delavirdine) (Dresser et al., 2000; Zhou et al., 2005). These inhibitors can boost the plasma concentration of themselves or other drugs that directly act on the hERG channel and enhance cardiotoxicity (Feng et al., 2018; Zhi et al., 2015). Among these drugs, ritonavir in lopinavir/ritonavir, which has been shown to be effective for the treatment of COVID-19 as a strong CYP3A4 inhibitor, can increase the oral bioavailability of certain HIV protease inhibitors, such as lopinavir (Dresser et al., 2000).

4. Drugs used in COVID-19

According to the guidelines, there are no safe and effective drugs to kill SARS-CoV-2. The validity of the drugs currently in clinical use, including CQ, HCQ, azithromycin, lopinavir/ritonavir, etc. (Table 1) was obtained from small clinical trials. Most of these studies have a relatively small sample size, and some of them have opposite results. Therefore, when these drugs are prescribed, both the results of current trials and the patient's condition, as well as possible serious adverse reactions, should be considered, and careful assessments and choices should be made until a comprehensive and reliable clinical trial is completed.

4.1. CQ and HCQ

CQ and HCQ are quinoline antimalarial drugs, among which CQ is

Table 1
Potential therapeutic drugs for COVID-19 and their adverse effect of QT prolongation.

Drug name	Effects on COVID-19	Assessments of the QT interval	Side effects on the hERG channel	References
CQ HCQ	Reduced viral load and the inhibition of SARS-CoV-2 in vitro.	QT prolongation resulting in TdP.	Blocked I_{Kr} current. Slowed rate of deactivation and increased transport of the hERG protein by CQ.	(Borsini et al., 2012; Gautret et al., 2020; Saleh et al., 2020; Sánchez-Chapula et al., 2001, 2002; Yao et al., 2020)
Azithromycin	Enhanced HCQ potency of viral elimination.	QT prolongation and increased risk of TdP in combination with CQ or hydroxychloroquine.	Blocked I_{Kr} current under high plasma concentration. No evidence of interference with hERG trafficking.	(Chorin et al., 2020; Gautret et al., 2020; Juurlink, 2020; Yang et al., 2017; Zhang et al., 2017)
Lopinavir/ritonavir	Reduced length of hospital stay for severe patients.	Potential QT prolongation.	hERG channel blockade. No evidence of interference with hERG trafficking.	(Anson et al., 2005; Cao et al., 2020a)

the most widely used antimalarial drug in history (Haeusler et al., 2018). In the treatment of COVID-19, CQ and HCQ have attracted a great deal of interest. An open-label, non-randomized study involving the application of HCQ (combined with azithromycin in some patients) showed that HCQ treatment is significantly associated with reduced/disappeared viral load in COVID-19 patients (Gautret et al., 2020). A small, prospective, observational study also suggested that CQ/CQ $\pm$ azithromycin may be effective in controlling SARS-CoV-2 infection, but the use of these drugs alone or in combination may prolong the QT interval and therefore increase the incidence of TdP (Saleh et al., 2020). An in vitro study also found that CQ and HCQ were effective in controlling SARS-CoV-2 infection (Wang et al., 2020), and HCQ was more effective than CQ in inhibiting SARS-CoV-2 (Yao et al., 2020).

There are now more than 100 clinical trials aimed at testing CQ or HCQ in the treatment of COVID-19, and CQ and HCQ have even been used as standard treatments for COVID-19 patients in hospitals in some countries, such as China (Ledford, 2020). Unfortunately, CQ publicity is derailing the search for coronavirus treatments, even leading to difficulty in treating patients with autoimmune diseases, which can result in potentially life-threatening manifestations, such as lupus nephritis (Jakhar and Kaur, 2020; Ledford, 2020; Yazdany and Kim, 2020). Despite this situation, the data supporting the treatment of COVID-19 with CQ or HCQ are limited (Ledford, 2020; Moore, 2020; Yazdany and Kim, 2020). And as mentioned earlier, a large RCT showed that COVID-19 patients receiving HCQ treatment did not benefit, or even be harmful (Horby et al., 2020). The NIH noted that there are insufficient data to recommend or oppose the use of CQ and HCQ for COVID-19 populations, and in COVID-19 patients receiving HCQ or azithromycin, 11%–25% of them have excessively prolonged QT intervals (i.e., greater than 500 ms) (Chorin et al., 2020; Panel, 2020). Therefore, better RCTs of CQ or HCQ are needed to effectively treat COVID-19 (Ferner and Aronson, 2020).

It is well known that antimalarial drugs are cardiotoxic (White, 2007), and QT prolongation is the most common adverse reaction to antimalarial drugs (Llanos-Cuentas et al., 2014). Although small doses of CQ and HCQ are generally safe, both can block the hERG channel (Giudicessi et al., 2020; Naksuk et al., 2020). Long-term use of CQ and HCQ has been reported to induce QT prolongation and malignant arrhythmia (Chen et al., 2006; Stas et al., 2008), and CQ-induced TdP in a COVID-19 patient was also reported (Szekely et al., 2020). Antimalarial drugs likely block the hERG channel in heterologous expression models and animal models (Sánchez-Chapula et al., 2001; Traebert et al., 2004). In feline ventricular cardiomyocytes, CQ blocked several inward and outward membrane currents, and the order of potency is inwardly rectifying potassium current $(I_{K1})> I_{Kr} > I_{Na} > I_{CaL}$ (Sánchez-Chapula et al., 2001). In contrast, CQ significantly slowed the rate of hERG channel deactivation, reflecting the inability of drug-bound channels to close (Sánchez-Chapula et al., 2002). Furthermore, as reported by hERG-lite (Wible et al., 2005), a novel systematic high-throughput screen for diLQTS risk, CQ increases hERG protein transport (Borsini et al., 2012). These different results indicate that a more sophisticated intracellular view to illuminate hERG channel

inhibition induced by CQ is required. In addition, both CQ and HCQ are metabolized by CYP3A4, and the risk of QT prolongation might increase if CQ and/or HCQ are combined with CYP3A4 inhibitors such as ritonavir/lopinavir or azithromycin (Naksuk et al., 2020; Wu et al., 2020).

4.2. Azithromycin

Azithromycin, as a macrolide antibiotic, is thought to enhance the therapeutic effect of HCQ in COVID-19 patients (Gautret et al., 2020). Similarly, a combination of azithromycin and CQ/HCQ was shown to be helpful for COVID-19 patients, and there were no reports of death from fatal arrhythmia (Saleh et al., 2020). However, given the cardiotoxicity of antimalarial drugs themselves, whether azithromycin when combined with them increases adverse reactions and whether we should use these drugs alone or in combination to treat COVID-19 is worth considering. As previously mentioned in a cohort study, the effect of azithromycin combined with CQ/HCQ on prolonging the QT interval is more obvious (Mercuro et al., 2020), and approximately one-quarter of the QT interval is prolonged excessively (Chorin et al., 2020). Perhaps azithromycin itself does not usually cause a clinically significant prolongation of the QT interval (Thomsen et al., 2006), but its use in combination with CQ or HCQ may theoretically increase the risk of TdP (Juurlink, 2020). These conflicting and poor-quality studies suggest that clinicians should carefully weigh the risks and benefits of azithromycin, CQ and HCQ, and it may be advisable to avoid these drugs.

Among macrolides, azithromycin is considered to be the least likely to cause arrhythmia because it is the least cardiotoxic, with an estimated 47 added cardiovascular deaths per million courses according to a report (Ray et al., 2012). Indeed, studies have confirmed that the rank order of arrhythmogenicity is estimated to be erythromycin > clarithromycin > roxithromycin > azithromycin (Milberg et al., 2002; Ohtani et al., 2000). Specifically, azithromycin suppresses the I_{Kr} current only at 50 times the clinically related concentration (2075 mg/L), and the inhibition rate is approximately 30% (Zhang et al., 2017). Unsurprisingly, compared with dofetilide, which has been proven to be an hERG channel blocker, azithromycin has no electrophysiological effects; thus, azithromycin is safe (Avedissian et al., 2019; Thomsen et al., 2006). However, based on the evidence of macrolides (such as erythromycin) targeting hERG channels (Volberg et al., 2002), it is necessary to further investigate the interaction of azithromycin with the hERG channel, even though azithromycin mainly increases cardiac Na^+ current and only slightly blocks I_{Kr} (Yang et al., 2017). Moreover, azithromycin, as a weaker CYP3A4 inhibitor than homologous antibiotics, may increase the risk of QT prolongation when used in combination with antimalarial drugs in treating COVID-19 patients (Wu et al., 2020). This seems to explain why azithromycin in combination with CQ or HCQ has a more significant QT prolongation effect.

4.3. Lopinavir/ritonavir

The HIV protease inhibitor class of antiretroviral drugs has obvious benefits for HIV. As an important CYP3A4 inhibitor, ritonavir can

enhance the effect of other protease inhibitors, such as lopinavir and atazanavir (Soliman et al., 2011; Zhou et al., 2005). The combined preparation of lopinavir/ritonavir has aroused widespread interest after a clinical trial for its use in COVID-19 was conducted (Cao et al., 2020a). The randomized trial found that for severe COVID-19 patients, lopinavir/ritonavir (400 mg and 100 mg, respectively) treatment does not significantly promote clinical improvement, reduce mortality or reduce the detectability of throat RNA of SARS-CoV-2, but it is beneficial for some secondary outcomes (e.g., a shorter time to stay in the intensive care unit (ICU)) (Cao et al., 2020a; Stower, 2020). Subsequently, although researchers advocated that lopinavir/ritonavir can be used as an alternative treatment for COVID-19 before the completion of the World Health Organization SOLIDARITY trial (Cao et al., 2020b), the side effects, including QT prolongation, have raised concerns about the higher dose or longer treatment of this programme. It is uncertain whether lopinavir/ritonavir and other antiretroviral drugs can ameliorate clinical outcomes or prevent infection in patients with high-risk COVID-19 (Ford et al., 2020). More recently, it has been reported that a triple combination of interferon beta-1b, lopinavir/ritonavir, and ribavirin is safer than and superior to lopinavir/ritonavir alone in alleviating symptoms in patients with mild to moderate COVID-19 (Hung et al., 2020). However, the same question regarding how to balance the risks and benefits remains.

The evidence for HIV protease inhibitor-induced arrhythmia is sufficient (Anson et al., 2005; Cao et al., 2020a; Gallagher et al., 2008; Han et al., 2015; Kikuchi et al., 2002; Soliman et al., 2011; Vicente et al., 2019). In vitro, lopinavir, nelfinavir, ritonavir, and saquinavir caused dose-dependent hERG channel blockade (Anson et al., 2005). A RCT showed that treatment with ritonavir-enhanced protease inhibitors and non-enhanced regimens had similar effects on QT duration (Soliman et al., 2011), suggesting that combined treatment regimens may be more beneficial with fewer side effects, and for QT prolongation, the role of ritonavir as an enhancer might not be as important. In particular, 100 mg ritonavir did not cause QT prolongation in healthy subjects (Sarapa et al., 2008); therefore, as a CYP3A4 inhibitor, it may generate side effects only when it increases the blood concentration of related drugs.

Except for atazanavir, there is no relevant evidence to support whether other protease inhibitors affect hERG protein maturation and expression on the plasma membrane (Han et al., 2015). It has been confirmed that HIV protease inhibitors induce ER stress (ERS) in intestinal epithelial cells (Wu et al., 2010), and importantly, ERS can downregulate cardiac ion channel expression (Liu et al., 2018). Referring to the effect of rosuvastatin on the hERG channel (Feng et al., 2019), ERS may play an important role in diLQTS. Whether the hERG channel is affected by COVID-19-related drugs through ERS requires further verification.

5. Future directions

Various factors can affect the hERG channel to induce QT prolongation, and QT prolongation may also be the result of multiple ion channel actions. In the course of COVID-19, in addition to affecting the lungs, causing interstitial pneumonia and severe acute respiratory distress syndrome (ARDS), SARS-CoV-2 also damages multiple organs due to a massive increase in inflammatory factors, especially in the cardiovascular system, leading to a variety of cardiac problems such as arrhythmia and myocarditis (Guzik et al., 2020; Inciardi et al., 2020; Zheng et al., 2020). In such cases, the cardiotoxicity of relevant therapeutic drugs may be obscured by the disease itself; therefore, it is necessary to conduct comprehensive clinical management to consider whether to use these drugs, and if necessary, to monitor ECGs. Most drug interactions with the hERG channel induce a prolonged QT interval, which is considered a major risk factor in pharmaceutical drug development, and in addition to the hERG channel, drugs actions on many ion channels causing severe arrhythmias have become a limiting factor for their clinical use (Denning et al., 2016). Therefore, it may be necessary

to determine the cardiotoxicity of a drug before it enters clinical use in the treatment of COVID-19, which requires a sensitive and effective experimental platform to carry out rigorous in vitro experiments as well as tremendous effort for preclinical management.

In 2013, the U.S. FDA proposed an international initiative termed the Comprehensive In Vitro Proarrhythmia Assay (CiPA), which recommends that a multi-electrode array (MEA) be used as a measurement tool, combined with human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), to conduct a preclinical assessment of a drug to evaluate the risk of TdP. The CiPA initiative requires a comprehensive ion current effect, not just I_{Kr}, to evaluate preclinically drug safety, and hiPSC-CMs will become a new chapter in safety assessment guidelines (Denning et al., 2016). Compared with heterologous systems and animal models in research on cLQTS or diLQTS, hiPSC-CMs, as an autologous source of reprogrammed cells, show a major advantage. Although still immature (Veerman et al., 2015), hiPSC-CMs almost completely reproduce the phenotype of cardiomyocytes in vitro because they contain multiple ion channels that participate in the action potentials of cardiomyocytes (Ma et al., 2011). The results of hiPSC-CMs for proarrhythmia prediction under CiPA would serve as predictive indicators for the ion channel and *in silico* modelling prediction of proarrhythmic risk (Blinova et al., 2017). More importantly, individual-derived somatic cells with gene mutations can also be reprogrammed to differentiate into disease-specific cardiomyocytes, such as LQTS-hiPSC-CMs (Egashira et al., 2012; Itzhaki et al., 2011; Portero et al., 2017; Sala et al., 2019; Wuriyanghai et al., 2018) and Brugada syndrome (BrS)-hiPSC-CMs (Belbachir et al., 2019; Kosmidis et al., 2016), from LQTS and BrS patients, respectively, which has considerable significance for the study of gene-drug interactions. An MEA is a high-throughput screening tool for cellular electrical activity, whose measured field potential duration (FPD) reflects the QT interval and, to some extent, the activities of various ion channels (Nozaki et al., 2014).

With the combination of hiPSC-CMs and MEAs, many drugs can be screened sensitively and efficiently (Nozaki et al., 2014), with great potential and advantages in reducing the cost of drug development compared with the use of immortalized cell lines or animal models. Furthermore, disease-specific hiPSC-CMs can be used to detect effective treatments in vitro that can be effectively translated into clinical trials (Mehta et al., 2018; Schwartz et al., 2019). In the future, related work should focus more on systemizing and standardizing hiPSC-CMs/MEA applications for comprehensive preclinical drug safety screening and generating systematic, large-scale, and available drug safety data to further guide clinical practice. For drugs that must be used but are cardiotoxic, inducing QT prolongation, it is still necessary to further clarify the molecular mechanism behind possible rescue strategies. LUF7346, as an hERG channel allosteric modulator, was recently shown to reverse congenital and drug-induced hERG channel blockade in hiPSC-CMs and heterologous expression models through binding to sites in the channel that are different from traditional drug-binding sites to induce a conformational change in the channel (Sala et al., 2016). However, an excessively shortened QT interval caused by related rescue strategies is also a problem worthy of attention. In summary, the goal of precision medicine may be truly achieved through clinical translation studies only after a comprehensive assessment of risks and benefits as well as a deeper understanding of underlying mechanisms.

CRediT authorship contribution statement

Zheng Zequn: Conceptualization, Data curation, Writing - original draft, Software, Resources. **Wu Yujia:** Conceptualization, Data curation, Writing - original draft, Software, Resources. **Qian Dingding:** Investigation, Supervision. **Lian Jiangfang:** Conceptualization, Writing - review & editing.

Declaration of competing interest

None.

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