Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
It is time to drop hydroxychloroquine from our COVID-19 armamentarium

Tarek Kashour\textsuperscript{a}, Imad M. Tleyjeh\textsuperscript{b,c,d,e,*}

\textsuperscript{a} Department of Cardiac Sciences, King Fahad Cardiac Center, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia
\textsuperscript{b} Infectious Diseases Section, Department of Medical Specialties, King Fahad Medical City, Riyadh, Saudi Arabia
\textsuperscript{c} Division of Infectious Diseases, Mayo Clinic College of Medicine and Science, Rochester, MN, USA
\textsuperscript{d} Department of Epidemiology, Mayo Clinic College of Medicine and Science, Rochester, MN, USA
\textsuperscript{e} College of Medicine, Al Faisal University, Riyadh, Saudi Arabia

A B S T R A C T

Chloroquine (CQ) and hydroxychloroquine (HCQ) were among the first drugs repurposed for the treatment of SARS-CoV-2 infection. A few in vitro studies confirmed that both drugs exhibited dose dependent anti-SARS-CoV-2 activities. These observations and the encouraging results from early poorly conducted observational studies created a major hype about the therapeutic potential of these drugs in the treatment of COVID-19 disease. This was further catalyzed by media and political influences leading to a widespread use of these agents. Subsequent randomized trials revealed lack of efficacy of these agents in improving the outcomes of COVID-19 or in preventing infection in post-exposure prophylaxis studies. Nevertheless, many ongoing trials continue to actively recruit tens of thousands of patients to receive HCQ worldwide. In this perspective, we address the possible mechanisms behind the lack of efficacy and the increased risk of cardiac toxicity of HCQ in COVID-19 disease. For the lack of efficacy, we discuss the fundamental differences of treatment initiation between in vitro and in vivo studies, the pitfalls of the pharmacological calculations of effective blood drug concentrations and related dosing regimens, and the possible negative effect of HCQ on the antiviral type-I interferon response. Although it has been repeatedly claimed that HCQ has a longstanding safety track record for many decades in use, we present counterarguments for this contention due to disease-drug and drug-drug interactions. We discuss the molecular mechanisms and the cumulative epidemiological evidence of HCQ cardiac toxicity.

Introduction

Because of their long-standing known in vitro antiviral activity, antimalarials chloroquine (CQ) and hydroxychloroquine (HCQ) were among the first medications that were repurposed for the treatment of COVID-19 disease. Indeed, in vitro anti-SARS-CoV-2 effects of CQ/HCQ have been demonstrated in a few studies [1-3]. Hashem et al [4] recently reviewed the possible molecular sites of action of CQ/HCQ as SARS-CoV-2 antiviral agents. HCQ can inhibit cellular entry of SARS-CoV-2 by interfering with the glycosylation of its cellular angiotensin converting enzyme 2 (ACE2) receptor. HCQ can also affect the early stages of viral replication by inhibiting virus-endosome fusion, likely via increasing endosomal pH [4].

Furthermore, early clinical studies in COVID-19 patients, although with methodological flaws, reported less severe pneumonia, shorter disease course and faster viral clearance in response to CQ therapy [5] and reduced nasopharyngeal viral carrier rate with HCQ and azithromycin treatment [6]. These limited data along with media and political influences led to a wide adoption of CQ/HCQ as a therapeutic option for COVID-19. Countries filled their national stockpiles with HCQ and included it in their treatment guidelines while the drug was being studied in clinical trials. In USA, for example, there was a major increase in CQ/HCQ prescriptions of approximately 2000% [7]. However, early hopes started to dissipate in June when the US Food and Drug Administration revoked permission for the drug to be distributed to treat COVID-19 after preliminary negative findings from the RECOVERY trial, leaving the US federal government stuck with 63 million doses of hydroxychloroquine [8].

Although large randomized controlled trials (RCTs) were started worldwide, a few were either stopped early for futility or showed no benefits [9-11]. Moreover, two recent RCTs for post-exposure prophylaxis did not find any significant decrease in risk of COVID-19 [12,13]. Conflicting data from cohort studies and RCTs [9-11] about the efficacy and safety of CQ/HCQ in COVID-19 started to emerge. Our group conducted a systematic review and meta-analysis of reported observational studies and RCTs that included 22 studies with 21,615 COVID-19 patients. We observed, with moderate certainty evidence, that HCQ, with or without AZ, lacks efficacy in reducing short-term mortality in patients hospitalized with COVID-19 or risk of hospitalization in outpatients with COVID-19 [14]. Moreover, we reported in another recent meta-analysis that CQ/HCQ therapy in COVID-19 patients was associated with a significant increased risk of QT prolongation, drug discontinuation, arrhythmias, and other cardiac toxicities [15].

Nevertheless, despite the cumulative evidence against the benefit of HCQ in COVID-19 patients, there are at least 72 ongoing RCTs...
worldwide actively recruiting patients to receive HCQ vs. other control groups as of July 28, 2020, with a total of 121,272 patients planned to be enrolled in these trials (https://clinicaltrials.gov/). For example, funded by the COVID-19 Bill & Melinda Gates Foundation, Wellcome and Mastercard Therapeutics Accelerator grant, the COVICOV study is ongoing and will enroll around 40,000 health care workers who have close contact with COVID-19 patients to determine whether CQ or HCQ are effective in preventing COVID-19.

In this perspective, we discuss the possible reasons and mechanisms for the lack of efficacy and increased cardiac toxicity of HCQ in the context of COVID-19 disease.

### Efficacy shortcomings

The discordant findings of the in vitro anti-SARS-CoV-2 effects of CQ/HCQ and their clinical inefficacy are concordant with previous observations from several other viral infections’ studies. Three main reasons could explain this discrepancy.

#### Timing of initiation of HCQ

Most of the in vitro studies employed pre-treatment protocols where cells are treated with the drug of choice before inoculation with the tested virus. In vitro studies that compared pre and post-infection CQ/HCQ treatment have demonstrated less effective antiviral activities in the post-infection experiments [3,16-18]. Yao et al tested the antiviral effects of CQ and HCQ against SARS-CoV-2 virus in Vero E6 cells. They noticed a superior antiviral effect when the cells were pre-treated with CQ or HCQ two hours before infection in comparison to adding the drugs two hours after the infection. In another recent study, HCQ at concentrations of 1–2 mg/ml did not have a significant anti-SARS-CoV-2 activity when added one hour after inoculation of Vero E6 cells with SARS-CoV-2 virus [16]. Similarly, Vincent et al examined the effect of CQ against SARS-CoV using different drug concentrations in a pre and post-infection experiments. CQ at 0.1, 1.0 and 10 μM, added 20–24 h before the infection, decreased infectivity by 28%, 53% and 100%. However, when CQ was added 3–5 h after infecting the cells, higher concentrations of CQ of up to 50 μM were needed to decrease infectivity [17]. Similar observations were reported with MERS-CoV virus where CQ effectively inhibited virus production if added prior to infection of Vero E6 cells but failed to reduce virus production if added one-hour post-infection [18]. These observations indicate that the main mechanism of action of CQ/HCQ is at the early stages of viral infection, namely, at the adherence and entry stages to the host cells. Therefore, achieving viral control with CQ/HCQ might not be feasible since SARS-CoV-2 viral load peaks early with symptom onset [19,20].

#### Subtherapeutic clinical dosing regimens and narrow therapeutic index

The translation of in vitro antiviral activity to appropriate clinical dosing regimens is very complex. The in vitro half-maximal effective antiviral concentrations (EC50) values of CQ/HCQ reported in the literature were based on extracellular drug concentrations present in cell culture media. CQ/HCQ have a large volume of distribution and long plasma elimination times and have been shown to achieve very high lung tissue concentrations reaching over 600 times that of plasma [21] and this has served as the rationale to support CQ/HCQ as an experimental regimen against SARS-CoV-2.

The reported in vitro EC50 for CQ and HCQ varied widely and, in the case of SARS-CoV-2, the EC50 for QC and HCQ ranged between 1.13 and 7.36 μM, and 0.72 and 17.31 μM, respectively [4]. The lowest EC50 of 0.72 μM for HCQ reported by Yao et al in their post-infection experiments, was much lower than the lowest EC50 of 5.85 μM in their pre-treatment experiments [3] and from that reported by all other investigators [4]. The lowest EC50 from Yao et al. experiments was used to estimate the predicted minimum blood concentration of HCQ needed for effective antiviral effect against SARS-CoV-2 virus. Based on their physiologically based pharmacokinetic models and simulation results, they recommended a loading dose of 400 mg twice daily of oral HCQ, followed by a maintenance dose of 200 mg given twice daily for 4 days for SARS-CoV-2 infection. This study received wide attention and hundreds of citations within two months. However, the HCQ dosing regimens recommended by Yao et al. were based on the ratios of free lung trough concentration to the in vitro EC50 values. Although HCQ has very high tissue to plasma ratio, this high tissue concentration is due to sequestered drug inside acidic cellular organelles. CQ/HCQ are known to accumulate in endosomes, Golgi apparatus and lysosomes (Reviewed by [21]). In fact, it has been calculated that the lysosomal HCQ concentration can reach 80 μM while extracellular concentrations were around 0.5 μM [22]. Thus, these EC50 values should have been compared with in vivo free drug concentration in the plasma rather than in lung tissue.

Based on this rationale, Fan et al. re-calculated the ratios of free lung extracellular trough concentrations, which were assumed to be similar to the free plasma concentrations, to the in vitro EC50 value. They observed that the calculated free lung concentrations that would result from proposed dosing regimens by Yao et al. are well below the in vitro EC50 values; suggesting that current dosing regimens lack the antiviral effect against SARS-CoV-2 and making it unlikely to achieve antiviral activity with a safe oral dosing regimen [23]. Garcia-Cremades et al. also made calculation for the predicted plasma antiviral EC50 of HCQ and found it to be 4.7 μM (1.58 mg/ml), which is much higher than the original estimates of Yao et al. [24]. They predicted that HCQ of > 400 mg twice a day for 5 days or more are necessary to achieve this plasma concentration. This higher dose regimen could significantly increase the risk of QT prolongation [24].

Despite the above dosing considerations, a review of all ongoing actively recruiting RCTs registered on clinicaltrials.gov as of July 28, 2020, revealed only a single RCT using HCQ 800 mg loading dose on day 1 and followed by 400 mg twice daily for 6 days. The majority of other treatment RCTs used the dose suggested by Yao et al [3] or even lower doses. The few prevention RCTs used lower doses.

It has been observed in mice models that high dose of 90 mg/kg of CQ given twice a day was required to achieve a steady-state blood level of 2.5 mg/ml [25]. Adopting high dose CQ/HCQ regimens in humans would increase the risk of adverse events significantly, as was experienced in a recent RCT of high dose QC in COVID-19 patients, that was stopped early for harm [26]. Additionally, the optimal CQ or HCQ blood levels for effective antiviral action is at large unknown, and the human studies correlating CQ/HCQ blood levels and clinical response in viral illnesses and other diseases are limited. For example, Sperber et al reported a wide range of HCQ blood concentrations of 0.27–1.0 mg/ml in 40 HIV-1 patients treated with HCQ 800 mg/day for 8 weeks [27]. They noticed favourable outcomes only in those patients who achieved the highest HCQ blood concentrations [27]. Similar trends between HCQ levels and clinical response were noted in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis [28,29].

A recent study by Balevic et al. evaluated serum and plasma HCQ concentration from published studies and serum samples of pediatric SLE patients treated with HCQ, as well as simulated concentrations based on published pharmacokinetics [30]. They found that in all included studies, the average serum/plasma HCQ concentration were below the lowest antiviral target levels for SARS-CoV-2 of 0.48 mg/ml that were observed by Yao et al [30]. Two other small studies examined the pharmacokinetics of HCQ in COVID-19 patients [6,31]. Gautret et al. measured HCQ blood levels in 20 COVID-19 patients treated with HCQ 600 mg/day and found that the mean HCQ blood concentration was 0.46 mg/ml [6]. These levels were below the lowest estimated levels of 0.48 mg/ml based on the lowest effective in vitro concentration of 0.72 μM. In another study, Perinel et al determined HCQ blood levels in 13 COVID-19 patients admitted to intensive care unit and...
treated with HCQ 600 mg/day. They observed that only 61% of them achieved what they considered the minimum therapeutic concentration of 1 mg/ml with the mean time to reach this concentration of 2.7 days [31]. These studies indicate that even using the lowest in vitro HCQ inhibitory concentration, achieving minimum clinical therapeutic concentration of HCQ seems not possible.

HCQ negative effect on type I interferon response

Type I interferon response plays a critical role in early suppression of viral replication. Channappanavar et al. [32] used a SARS-CoV-1 animal model to describe how rapid and robust virus replication with delayed IFN-I can lead to lung immunopathology, with fatal outcomes. Recently, investigators reported on an integrated immune analysis on a cohort of 50 COVID-19 patients with various disease severity [33]. They observed a unique phenotype in severe and critical patients, consisting of a highly impaired type I interferon response, associated with a persistent blood viral load and an exacerbated inflammatory response. It is well established that antimalariaal drugs have solid anti-inflammatory and immunomodulatory effects. Among these long-term effects are their ability to decrease the production of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-a), interleukin-1 beta (IL-1b) and interleukin-6 (IL-6), and improve endothelial function and reduce prothrombotic state [34,35]. These effects could potentially be beneficial in patients with severe COVID-19 disease associated cytokine storm. However, HCQ has been shown to reduce the affinity of toll-like receptor 7 and 9 (TLR7 and TLR9) to viral RNA and to inhibit cyclic GMP-AMP synthase (cGAS) pathway and thereby inhibit type I interferon response [34]. This blunting effect on type I interferon response might counteract the direct antiviral effects of HCQ, which provides another reason for the lack of efficacy of HCQ in controlling SARS-CoV-2 infection.

Significant cardiac toxicity concerns

Although it has been repeatedly claimed that HCQ has a long-standing safety track record for many decades in use, this contention is not applicable in COVID-19 patients due to disease-drug interactions and drug-drug interactions. Moreover, several studies have reported an increased risk of cardiac toxicity among COVID-19 patients treated with CQ/HCQ. We have shown in a recent meta-analysis that CQ/HCQ treatment in COVID-19 increased the risk of QTc prolongation and discontinuation of drug due to QT prolongation. In addition, the risk of torsades de pointes ventricular tachycardia (TdP), or monomorphic ventricular tachycardia or cardiac arrest was 3 per 1000 (95% CI 0.0-21) [15]. Although, in absolute terms, the incidence of TdP was low, it was higher than the reported incidence for some drugs that were withdrawn from the market such as cisapride. We have also found an increased risk of other arrhythmias and other cardiac complications [15].

The principal mechanism responsible for QT prolongation produced by CQ and HCQ is due to blocking of the KCNQ1-encoded hERG/Kv11.1 potassium channel, which is responsible for the rapidly-activating potassium current (I(Kr)). This rapidly-activating current along with the slowly-activating current (I(Ks)) are responsible for pumping potassium ions outside cardiomyocytes. This outward potassium current after the plateau phase (phase 2) of the action potential results in rapid repolarization phase of the action potential (phase 3) [36]. Genetic mutations in the genes encoding these potassium channels as well as drug-blockage of hERG/Kv11.1 potassium channels result in prolongation of the cardiac action potential that manifests as prolonged QT interval on the surface electrocardiogram [36]. The intracellular face of the hERG channel is large and is lined with a number of aromatic residues allowing drugs like CQ and HCQ and others to bind to this part of the channel and block the outward potassium current [36,37]. In a recent study using ex-vivo guinea pig and rabbit heart models, it was shown that HCQ resulted in the generation of repolarization alternans and precipitated polymorphic ventricular tachycardia [38]. It is also important to take in consideration that the prevalence of congenital long QT syndrome (LQTS) is approximately 1 in 2000 people worldwide. Importantly, many individuals with LQTS have normal baseline QTc values, but their risk of drug-induced QT prolongation and lethal arrhythmias is increased substantially. Furthermore, 8% of individuals of African descent (p.Ser1103Tyr-SCN5A) and 2% of individuals of European descent (p.Asp854Asn-KCNNE1) possess potentially pro-arrhythmic common variants associated with an increased risk of drug-induced long QT and sudden cardiac death [39]. Although the percentage of people with an inherent genetic risk is small (roughly 10%), the fact that SARS-CoV-2 infection has been spreading widely across the globe affecting millions of people, the total number of individuals at risk for drug-induced QT prolongation and TdP associated with indiscriminate use of CQ and HCQ may be unacceptably high [40].

It is important to note that patients with underlying cardiac diseases and comorbidities as well as inflammatory states are at increased risk of drug induced QTc prolongation [41]. Patients with severe COVID-19 disease usually have hypoxemia and may manifest hypotension and electrolyte imbalance and may need ICU admission; all of which have been shown to increase the risk of QTc prolongation in response to QT prolonging drugs [41–45]. moreover, COVID-19 patients manifest fever and raised interleukin-6 levels, which have been linked to increased risk of QT prolongation in response to drugs and inflammation [46,47].

HCQ use has also been associated with bradycardia. In a study of mouse atria, spontaneous beating was significantly reduced by HCQ. Similarly, these findings were confirmed in sinoatrial node cells from pigs with a clear dose-dependent effect [48]. This is important for patients who might be taking HCQ and concomitant beta-blockers or amiodarone. These combinations, especially in the setting of electrolyte imbalances, will result in significant reduction of the automaticity of the heart, and may lead to significant bradycardia. Finally, these drugs have active metabolites and relatively long elimination half-lives, especially in critically ill patients with multi-organ failure which might increase their arrhythmogenic risk [49].

It is also important to mention that it has been a common practice to increase HCQ in combination with azithromycin for COVID-19 during the current pandemic. Azithromycin has been identified as a potential cause of significant serious cardiac arrhythmias through QT prolongation dependent and independent mechanisms and has been linked to increased risk of sudden cardiac death [50,51]. Hence, the concomitant use of CQ/HCQ and azithromycin or other QT prolonging agents could potentially increase the risk of serious cardiac arrhythmias and death particularly in critically ill patients or those with risk factors for QT prolongation.

Increased risk of cardiac complications associated with the combination therapy of HCQ and azithromycin has also been reported in a recent preprint of a large population study of 956,374 users of HCQ. Among these patients, 323,122 were also treated with azithromycin. This combination therapy was associated with increased risk of 30-day cardiac mortality (CalHR 2.19, 95% CI 1.22–3.94), chest pain/angina (CalHR 1.15, 95% CI 1.05–1.26), and heart failure (CalHR 1.22, 95% CI 1.02–1.45) [52].

A recent study examined the prescription pattern of several drugs in USA and observed an almost 2000% increase in prescriptions for CQ and HCQ for fewer than 28 tablet fills for the week of March 15–21, 2020 in comparison with the same week in 2019. This surge remained steady during the following weeks [7]. This remarkable surge in CQ/HCQ use could lead to a substantial increase in preventable serious cardiac adverse events and mortality.

Conclusion

Treatment of SARS-CoV-2 infection with HCQ was not met with the expected success. This is probably related to its mechanism of action and the inability of the current dosing regimens to achieve the required
blood concentration necessary for effective antiviral activity. Moreover, HCQ monotherapy or in combination with azithromycin increased the risk of cardiac adverse events including QT prolongation, arrhythmias and other cardiac complications. It is time to move on and examine other potential therapeutics in our battle against the COVID-19 pandemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References:

[1] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30(3):269–71.
[2] Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020;6:16.
[3] Yao Y, Ye J, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020.
[4] Hashem AM, Alghamdi BS, Algaissi AA, et al. Therapeutic use of chloroquine and hydroxychloroquine in COVID-19 and other viral infections: A narrative review. Travel Med Infect Dis 2020;35:101735.
[5] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biostat Trends 2020;4(1):72–3.
[6] Gastrup T, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;105949.
[7] Vaduganathan M, van Meijgaard J, Mehra MR, Joseph J, O’Donnell CJ, Warraich HJ. Prescription fill patterns for commonly used drugs during the COVID-19 pandemic in the United States. JAMA 2020.
[8] Elizabeth Cohen WB. US stockpile stuck with 63 million doses of hydroxychloroquine. https://edition.cnn.com/2020/06/17/health/hydroxychloroquine-national-stockpile.shtml. Accessed.
[9] Porby P, Mathun M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19: Preliminary results from a multi-centre, randomised, controlled trial. medRxiv 2020;2020:2015. 2020.20151852.
[10] Mitjà O, Corbacho-Monné M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild COVID-19. A randomised-controlled trial. Clin Infect Dis 2020.
[11] Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adult outpatients with early COVID-19: A randomized trial. Ann Intern Med 2020.
[12] Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine: implications for rheumatology. Nat Rev Rheumatol 2020;9(2):92–9.
[13] Mitja O, Ubals M, Corbacho M, et al. A cluster-randomized trial of hydroxychloroquine as prevention of COVID-19 transmission and disease. medRxiv 2020;2020:2020. 2020.20157651.
[14] Kashour Z, Riaz M, Garabati M, et al. Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: A systematic review and meta-analysis. medRxiv 2020;2020:2020. 2020.20151110.
[15] Tleyjeh I, Kashour Z, AlDosary O, et al. The cardiac toxicity of chloroquine or hydroxychloroquine in COVID-19 patients: A systematic review and meta-regression analysis. medRxiv 2020;2020:2020. 2020.20132878.
[16] Kang CK, Seong MW, Choi SJ, et al. In vitro activity of lopinavir/ritonavir and hydroxychloroquine against severe acute respiratory syndrome coronavirus 2 at concentrations achievable by usual doses. Korean J Intern Med 2020;35(4):782–90.
[17] Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus replication in cell culture. Antimicrob Agents Chemother 2004;48(8):4875–84.
[18] de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved clinical antiviral for SARS-CoV-2. Antimicrob Agents Chemother 2020;64(9):2553–65.
[19] Yang Z, Prinsen JK, Bersell KR, et al. Azithromycin causes a novel proarrhythmic effect of hydroxychloroquine and chloroquine in rheumatoid arthritis–a cross sectional study. J Rheumatol 1993;20(11):1874–9.
[20] Tleyjeh I, Kashour Z, AlDosary O, et al. Hydroxychloroquine blood concentration in lupus nephritis: a determinant of disease outcome? Nephrol Dial Transplant 2018;33(9):1604–10.
[21] Balevic SJ, Hornik CP, Green TP, et al. Hydroxychloroquine in patients with rheumatic disease complicated by COVID-19: Clarifying target exposures and the need for clinical trials. J Rheumatol 2020.
[22] Perinel S, Saunay M, Botelho-Nevers E, et al. Towards optimization of hydroxychloroquine dosing in intensive care unit COVID-19 patients. Clin Infect Dis 2020.
[23] Channappanavar R, Fehr AR, Vijay R, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-Infected mice. Cell Host Microbe 2016;19(2):181–93.
[24] Tset SE, Day RO, Cutler DJ, et al. A systematic screen of FDA-approved drugs for inhibitors of biological threat agents. PLoS ONE 2013;8(4):e60579.
[25] Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A randomized clinical trial. JAMA Netw Open 2020;3(4):e208857.
[26] Sperber K, Louie M, Kraus T, et al. Hydroxychloroquine treatment of patients with human immunodeficiency virus type 1. Clin Ther 1995;17(4):622–36.
[27] Bedard NO, Day RO, Cutler DJ, et al. Concentration-effect relationship of hydroxychloroquine in rheumatoid arthritis—a cross sectional study. J Rheumatol 1993;20(11):1874–9.
[28] Cunha C, Alexander S, Ashby D, et al. Hydroxychloroquine blood concentration in lupus nephritis: a determinant of disease outcome? Nephrol Dial Transplant 2018;33(9):1604–10.
[29] Haugaa KH, Bos JM, Tarrell RF, Morlan BW, Caraballo PJ, Ackerman MJ. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. medRxiv 2020;2020:2020. 2020.20151852.
[30] Yang Z, Prinsen JK, Bersell KR, et al. Azithromycin and the risk of torsades de pointes: evidence from a large patient sample. May Clin Proc 2013;88(4):315–25.
[31] Pickham D, Hellenbrand E, Dobrin R, et al. High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: results of the QT in Practice (QTIP) Study. Crit Care Med 2012;40(2):394–9.
[32] Lamothé SM, Song W, Guo J, et al. Hyposxia reduces mature hERG channels through calcium-dependent up-regulation. Respir Res 2011;12(1):55.
[33] Landaß TD, Kaufmann B, Nussbaumer-Oechsner Y, et al. Patients with obstructive sleep apnea have cardiac repolarization disturbances when wakefulness: Randomized, placebo-controlled trial of acetazolamide. Sleep 2016;39(6):1613–7.
[34] Fernandes FM, Silva EP, Martins RR, Oliveira AG. QTc interval prolongation in critically ill patients: Prevalence, risk factors and associated medications. PLoS ONE 2018;13(6):e0199028.
[35] Giudicessi JR, Reden DM, Wilde AA, Ackerman MJ. Genetic susceptibility for COVID-19-associated sudden cardiac death in African Americans. Heart Rhythm 2020.
[36] Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for Coronavirus Disease 19 (COVID-19). Mayo Clin Proc 2020;95(6):1213–21.
[37] Haaga KH, Bos JM, Tarrell RF, Morlan BW, Caraballo PJ, Ackerman MJ. Institution-wide QT alert system identifies patients with a high risk of mortality. Mayo Clin Proc 2013;88(4):315–25.
[38] Aromolaran AS, Srivastava U, Ali A, et al. Interleukin-6 inhibition of hERG unblocking. Faseb J 2020;34(5):6027–48.
[39] Lane JCE, Weaver J, Kostka K, et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: A multinational, network cohort and self-controlled case series study. medRxiv 2020;2020:2020. 2020.20054551.