Ventricular arrhythmia risk due to Chloroquine in the treatment of COVID-19

Risque des troubles du rythme ventriculaire lié à la chloroquine dans le traitement de la Covid-19

Aymen El Hraiech[1,3], Imen Ben Ali[1,3], Saeb Ben Saad[2,3]

1- Hôpital Sahloul, Service de cardiologie - Tunisie
2- Hôpital Farhat Hached, Service de cardiologie – Tunisie
3- Université de Sousse, Faculté de Médecine Ibn El Jazzar Sousse- Tunisie

Résumé

L'infection au SRAS-CoV-2 est actuellement responsable d'une pandémie, avec des répercussions inédites sur le mode de vie des citoyens à travers le monde. La chloroquine, un antipaludéen, pourrait être une option pour le traitement de COVID-19. Cependant, la chloroquine peut allonger l'intervalle QT et exposer au risque d'une arythmie ventriculaire. Nous présenterons l'état des connaissances sur l'association entre l'utilisation de la chloroquine dans le traitement de COVID 19 et la survenue d'arythmie ventriculaire.

Mots-clés

Arythmie, Chloroquine, SARS-CoV-2, COVID-19, Tunisie.

Summary

Severe acute respiratory syndrome coronavirus 2 and associated lung disease COVID-19 has spread throughout the world and has become a pandemic. Chloroquine, an antimalarial drug, might be an option for treating COVID-19. However, chloroquine can prolong QT interval and thus expose to ventricular arrhythmia. We propose to summarize the state of knowledge on the association between ventricular arrhythmia and chloroquine in the treatment of COVID 19.

Keywords

Ventricular arrhythmia, Chloroquine, SARS-CoV-2, COVID-19, Tunisia.

Correspondance
Aymen El Hraiech
Hôpital Sahloul, Service de cardiologie - Tunisie

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel *Coronavirus* and associated lung disease COVID-19 has spread throughout the world and has become a pandemic. Facing the SARS-CoV-2, an unknown virus, an efficient approach to drug discoveries is to test whether the existing antiviral drugs are effective in the treatment of related viral infections.

Several antiviral drugs have been tested for efficacy inhibition SARS-CoV-2 replication in cell culture. The antimalarial drugs chloroquine (CQ) and his metabolite the hydroxychloroquine (HCQ) might be an option for treating COVID-19. Preliminary studies showed viral load reduction in COVID-19 patients treated with CQ or HCQ alone or in combination with azithromycin (1) (2). Even with little evidence, CQ and HCQ has been officially declared as a medical agents for COVID-19 in the seventh edition of the New *coronavirus* pneumonia diagnosis and treatment plan, released by the National Health and Care Commission of China on February 2020 (3). However, CQ can prolong QT interval and thus expose to a ventricular arrhythmia (VA) known as Torsades des pointes (TdP) (4).

This review focuses on the mechanism of CQ/HCQ induced QT prolongation, the risk factors for TdP, the association CQ/ HCQ and TdP and the prevention and monitoring of QT interval prolongation when CQ/HCQ is used to treat COVID-19.

METHODS

We performed a systematic electronic search using PubMed to identify relevant English-language articles published. Our search strategy used a combination of relevant keywords chosen according to the MeSH terms for CQ or HCQ, with subcategories such as ventricular arrhythmia, TdP, QT interval, QT prolongation, sudden death and cardiac toxicity. (‘‘hydroxychloroquine’’[MeSH] OR ‘‘chloroquine’’ [MeSH]) AND (‘‘ventricular arrhythmia’’ [MeSH] OR ‘‘Torsades de pointe’’ [MeSH] OR ‘‘QT prolongation’’ [MeSH] OR ‘‘QT interval’’ [MeSH] OR ‘‘sudden death’’ [MeSH] OR ‘‘cardiac toxicity’’ [MeSH]). Additional relevant articles were identified from the review of citations referenced and expert panel consensus supports.

RESULTS

QT interval measurement, physiology and mechanism of CQ or HCQ induced QT prolongation

The QT interval is defined as the interval from the onset of the QRS complex to the end of the T wave. It represents the period of time from the onset of ventricular depolarization (QRS complex) to the end, of ventricular repolarization (T wave) (5).

The QT interval is measured in leads showing the longest QT period, which is usually V2 or V3. If the T wave and U wave are superimposed or merged together, it is recommended to measure the QT interval in the leads not showing U waves, often aVR and aVL leads (6). Even with that, manual QT interval measurement is not an easy task (7). To an accurate ECG assessment of the QT interval, tangent method allows a reliable measurement (8). *(Figure 1)*

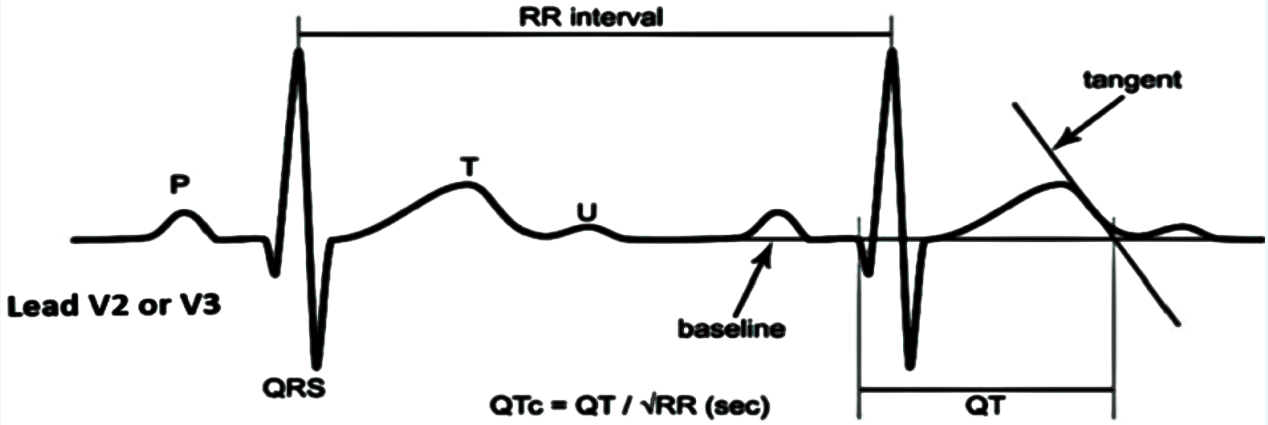

Figure 1: Manual QT interval measurement (5) (8)

Sequential electrocardiogram (ECG) recordings is also essential for identification of QT prolongation induced by pharmacological agents in drug studies. It is recommended to have uniform standardized ECG acquisition and a single reader responsible for overreading sequential tracings of an individual patient or research subject (5).

The QT interval varies with heart rate, autonomic tone, age, gender, and time of the day. Nevertheless, QT should be corrected. Corrected QT (QTc) is the QT interval corrected in one of several ways for heart rate. Many formulas have been proposed to adjust the QT interval for rate (8). The most widely used is Bazett's formula (9).

Wide QRS due to ventricular conduction abnormalities or ventricular pacing, prolongs the QT interval and, in this case, Bazett's formula has proven to be ineffective (10). Rautaharju's formula takes into consideration the width of the QRS in the calculation of the corrected QT and is, therefore, recommended in this case (11).

Another limit for Bazett's formula consists in both bradycardia and tachycardia but this could be overcome using Fridericia's Formula (12).

Web and smartphone applications have now made the use of these different formulas easier.

The QT interval represents the time of the ventricular depolarization and repolarization. It reproduces the summation of action potential (AP) of ventricular myocytes.

The AP reflects the flow of ion currents across a cell membrane through specialized channels made of protein complexes (13).

The mechanism of QT prolongation is almost always due to the blockage of the inward potassium rectifier (IKr) channel, also known as the hERG (ether a go go) channel. It conducts a rapid delayed rectifier potassium current, a critical current in the phase 3 repolarization of the cardiac AP (14).

In laboratory electrophysiological studies at low micromolar concentrations of CQ lengthened the AP of cat Purkinje fibers, and increased automaticity (15).

The CQ blocked the inward sodium current, the L-type calcium current, and potassium currents (15).

In clinical studies, both CQ and HCQ showed a prolongation in the QT interval. Indeed, after receiving 600 mg of CQ, we observe in adults a 16 ms mean prolongation of the QTc interval. Following the second dose of 600 mg, mean prolongation was 12 ms (16).

However, this effect is significantly attenuated with CQ/HCQ compared to quinidine and Halofantrine and other quinolone drugs (17).

Drug QT prolongation and arrhythmia: physiopathology and risk factors

The repolarization of ventricular myocardial cells is not a synchronous phenomenon resulting in a normal heterogeneity in refractory period among ventricular cells during the inscription of the T wave (18).

Any drug that increases the heterogeneity and dispersion of the ventricular repolarization prolongs the QT interval and then expose to VAs. Thus, quinolone's drugs use is associated with an increased susceptibility to VA and the occurrence of TdP. This has been mostly reported with Halofantrine (17). CQ/HCQ are known to have a less effect on QT prolongation and so, they are safer than others quinolones drugs (19).

However, the risk of TdP is not a linear function of QT interval duration nor the extent of change (20).

Many factors are associated with a high risk and predisposition to VA. These factors include female gender, elderly, structural heart diseases, congenital long QT syndrome, electrolyte imbalance (hypokalemia, hypomagnesaemia), abnormal hepatic or renal function and concomitant medications prolonging the QT interval (21) (22).

Tisdale et al.(23) have developed a risk score for predicting the risk of VA when prescribing drugs known with a QT prolongation effect.

American health authorities recommended to calculate this score before initiating treatment with CQ/HCQ in patients infected with SARS-CoV2 in order to orient the prescription (24).

Recently, the French society of cardiology has identified the risk factors of QT prolongation related to the prescription CQ/HCQ in COVID-19 (25). (Table 1)

Table 1 : Arrhythmia risk factors (25)

Modifiable factors	Combination of 2 drugs prolonging the QT interval
	Hypokalemia< 3.5 mmol/L
	Bradycardia< 50 bpm
	Hypocalcaemia< 2,2 mmol/L
Non-modifiable factors	Female
	Age>= 68 years old
	QTc on admission ECG >= 450ms
	Congenital long QT syndrome
	Sepsis
	Cardiac disease (ischemia, heart failure), renal failure, Hepatic insufficiency
Factors related to covid-19	Occurrence of hypokalemia
	Occurrence of renal failure
	Occurrence of cardiomyopathy
	Occurrence of arrhythmia

Table 2 : Arrhythmia risk classification due CQ/HCQ prescription (24) (25)

Low risk	Intermediate risk*	High risk*	Very high risk*
•Basic QTc <460 ms	•Basic QTc > 460 ms and < 480 ms	•Basic QTc > 480 ms	•Basic QTc > 500 ms
•Age <68 y	•Age ≥68 y	•History of ischemic cardiomyopathy or heart failure	•Congenital long QT syndrome
•Male sex	•Female sex	•Combination with QTc-prolonging drug	
•No cardiac history		•Renal failure	
•No abnormalities in lab test assessment		•Acute hepatitis	
		•Hypokalemia< 3.5 mmol/L	

Among these risk factors, a particular concern for hypokalemia, which is not unusual in the setting of sars cov2 infection considering the virus's action on the angiotensin converting enzyme 2 (ACE 2) and thereby the activation of the renin-angiotensin-aldosterone system.
These findings could then explain why hypokalemia is more frequent during this viral infection which seems to potentiate the inhibition of the IKr channels by chloroquine and increase QT interval lengthening (26).

CQ and HCQ and arrhythmia: real data world

Prolongation of the QT interval induced by CQ and HCQ has been associated with an increased incidence of sudden cardiac death (27) (28).
Despite this suggestive finding, CQ and HCQ as antimalarial drugs are prescribed and self-medicated on a vast scale in the tropical areas of the world, without reports of arrhythmic death under World Health Organization surveillance. Nonetheless, the absence of an active drug safety surveillance system in most of these countries limits reassurance from his safety use.
Thus, conclusive evidence of cardiotoxicity caused by these drugs is lacking and further pharmacovigilance is required.
Besides, the combination CQ or HCQ with azithromycin showed no additional arrhythmical ability (19).
A recently published study including 84 patients with COVID-19 treated with a combination of CQ or HCQ and azithromycin, a dangerous QT prolongation (QTc> 500 ms) was noted in 11% of the cases. COVID-19-related kidney failure was a major risk factor of QT prolongation. No serious arrhythmia was reported in this preliminary study (29). Chorin et al. suggested to monitor regularly the QTc interval 'in patients with SARS-CoV-2 infection treated with CQ or HCQ/ azithromycin association, particularly those with renal impairment, a common complication in patients with SARS-CoV-2 (29).
Recently, recommendations for the safe use of CQ and HCQ to treat COVID-19 have been published by the American College of Cardiology (24) and French society of cardiology (25). Several instructions should be followed before and during therapy prescription.

Safety use of CQ or HCQ for COVID-19 treatment

Because of TdP's potential lethality, the risk of QT prolongation has become a preoccupation in the prescription of CQ or HCQ for COVID-19 patients.
According to international recommendations (24) (25), an initial assessment before starting treatment with CQ / HCQ is mandatory. It includes an interrogation, an ECG with manual measurement of the QT interval and a blood test.
Afterwards, it is recommended to assess the risk of arrhythmia due to CQ/HCQ prescription.
Several ways are proposed for this risk assessment. American College of Cardiology recommended the use of Tisdale score (23), which is no specific for CQ/HCQ use. French Society of Cardiology identifies risk factors detailed in Table 1 and classifies them according to a severity scale.
Based on these two recommendations, we suggest an arrhythmia risk classification due CQ/HCQ prescription. (Table 2)
According to this arrhythmia risk classification, CQ/HCQ can be prescribed on an outpatient basis or in hospital, with or without monitoring. (Figure 2)
Figure 3 summarize the monitoring procedure for the safety use of CQ/HCQ in COVID-19.

CONCLUSION

The association between the use of Chloroquine and the occurrence of arrhythmia is not established. QT interval monitoring is mandatory if prescribed in at-risk patients. The prospective cohorts that are taking place worldwide will provide the answers to the safety of chloroquine in the treatment of COVID-19 as well as to the predictors of

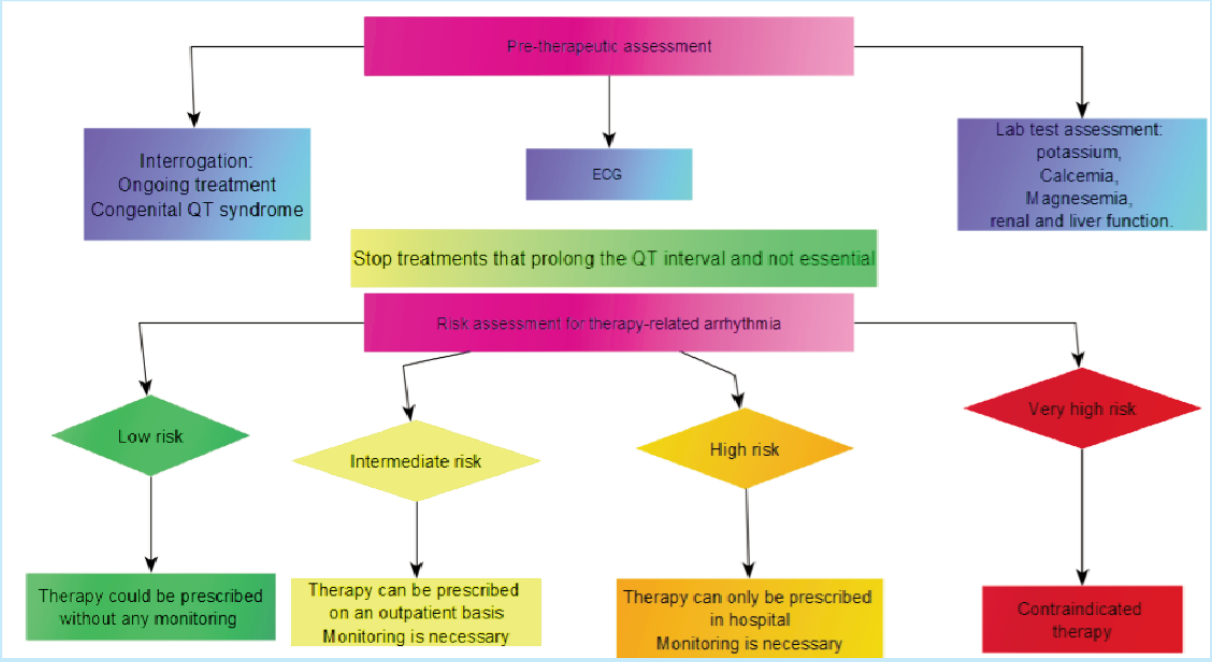

Figure 2: Arrhythmia risk assessment and decision of treatment diagram

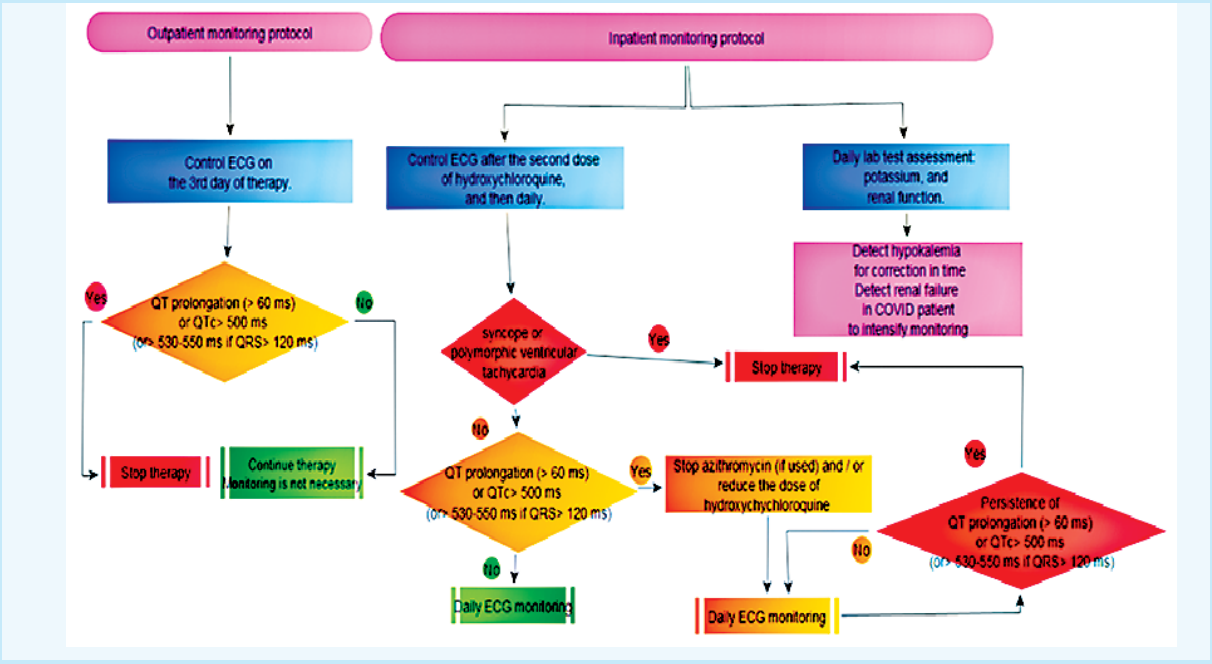

Figure 3: The monitoring procedure for the safety use of CQ/HCQ in COVID-19 patients

REFERENCES

1. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 20 mars 2020;105949.
2. Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents. 11 mars 2020;105938.
3. Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7) [Internet]. [cité 15 avr 2020]. Disponible sur: http://en.nhc.gov.cn/2020-03/29/c_78469.htm
4. El-Sherif N, Turitto G, Boutjdir M. Acquired Long QT Syndrome and Electrophysiology of Torsade de Pointes. Arrhythm Electrophysiol Rev. mai 2019;8(2):122‑30.
5. Rautaharju PM, Surawicz B, Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram: Part IV: The ST Segment, T and U Waves, and the QT Interval A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 17 mars 2009;53(11):982‑91.
6. Lepeschkin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram. Circulation. sept 1952;6(3):378‑88.
7. Viskin S, Rosovski U, Sands AJ, Chen E, Kistler PM, Kalman JM, et al. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. Heart Rhythm. juin 2005;2(6):569‑74.
8. Postema PG, De Jong JSSG, Van der Bilt IAC, Wilde AAM. Accurate electrocardiographic assessment of the QT interval: teach the tangent. Heart Rhythm. juill 2008;5(7):1015‑8.
9. Ahnve S. Correction of the QT interval for heart rate: review of different formulas and the use of Bazett's formula in myocardial infarction. Am Heart J. mars 1985;109(3 Pt 1):568‑74.
10. Evaluation de l'intervalle QT en présence d'un élargissement du QRS - Revue Médicale Suisse [Internet]. [cité 23 avr 2020]. Disponible sur: https://www.revmed.ch/RMS/2016/RMS-N-520/Evaluation-de-l-intervalle-QT-en-presence-d-un-elargissement-du-QRS
11. Rautaharju PM, Zhang Z-M, Prineas R, Heiss G. Assessment of prolonged QT and JT intervals in ventricular conduction defects. Am J Cardiol. 15 avr 2004;93(8):1017‑21.
12. Fridericia LS. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. Acta Medica Scandinavica. 1920;53(1):469‑86.
13. Titier K, Girodet P-O, Verdoux H, Molimard M, Bégaud B, Haverkamp W, et al. Atypical antipsychotics: from potassium channels to torsade de pointes and sudden death. Drug Saf. 2005;28(1):35‑51.
14. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. mars 2020;16(3):155‑66.
15. Sánchez-Chapula JA, Salinas-Stefanon E, Torres-Jácome J, Benavides-Haro DE, Navarro-Polanco RA. Blockade of currents by the antimalarial drug chloroquine in feline ventricular myocytes. J Pharmacol Exp Ther. avr 2001;297(1):437‑45.
16. Mzayek F, Deng H, Mather FJ, Wasilevich EC, Liu H, Hadi CM, et al. Randomized Dose-Ranging Controlled Trial of AQ-13, a Candidate Antimalarial, and Chloroquine in Healthy Volunteers. PLoS Clin Trials [Internet]. 5 janv 2007 [cité 14 avr 2020];2(1). Disponible sur: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1764434/
17. Nosten F, ter Kuile FO, Luxemburger C, Woodrow C, Chongsuphajaisiddhi T, White NJ, et al. Cardiac effects of antimalarial treatment with halofantrine. The Lancet. 24 avr 1993;341(8852):1054‑6.
18. Moore EN. Mechanisms and models to predict a QTc effect. The American Journal of Cardiology. 26 août 1993;72(6):B4‑9.
19. Fossa AA, Wisialowski T, Duncan JN, Deng S, Dunne M. Azithromycin/chloroquine combination does not increase cardiac instability despite an increase in monophasic action potential duration in the anesthetized guinea pig. Am J Trop Med Hyg. nov 2007;77(5):929‑38.
20. el-Sherif N, Turitto G. The long QT syndrome and torsade de pointes. Pacing Clin Electrophysiol. janv 1999;22(1 Pt 1):91‑110.
21. Chugh SS, Reinier K, Singh T, Uy-Evanado A, Socoteanu C, Peters D, et al. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: the Oregon Sudden Unexpected Death Study. Circulation. 10 févr 2009;119(5):663‑70.
22. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. Ther Adv Drug Saf. oct 2012;3(5):241‑53.
23. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes. juill 2013;6(4):479‑87.
24. Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19 [Internet]. American College of Cardiology. [cité 2 avr 2020]. Disponible sur: http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2farticles%2f2020%2f03%2f27%2 f14%2f00%2fventricular-arrhythmia-risk-due-to-hydroxychloroquine- azithromycin-treatment-for-covid-19
25. Préconisations cardiologiques | SFCardio [Internet]. [cité 17 avr 2020]. Disponible sur: https://sfcardio.fr/actualite/preconisations-cardiologiques?fbclid= IwAR2m_ZVbBpF 8L6bu6wa M5duNG0eREy2fP16 Tifz98Am VO3C0Umx2Zguq6fU
26. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med. 23 avr 2020;382(17):1653‑9.
27. Molokhia M, Pathak A, Lapeyre-Mestre M, Caturla L, Montastruc JL, McKeigue P. Case ascertainment and estimated incidence of drug-induced long-QT syndrome: study in Southwest France. Br J Clin Pharmacol. sept 2008;66(3):386‑95.
28. White NJ. Cardiotoxicity of antimalarial drugs. Lancet Infect Dis. août 2007;7(8):549‑58.
29. Chorin E, Dai M, Shulman E, Wadhwani L, Bar Cohen R, Barbhaiya C, et al. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin [Internet]. Cardiovascular Medicine; 2020 avr [cité 17 avr 2020]. Disponible sur: http://medrxiv.org/lookup/doi/10.1101/2020.04.02.2004705