

## QTc prolongation during the SARS-CoV-2 outbreak: clinical risk management through hospital training course, focus on elderly patients

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### Abstract

The recent outbreak exposed doctors to a new challenge: treating people without any scientific evidence. All molecules combined in treatment schedules were merged on the basis of weak and anecdotal data so, the recommendations are constantly changing. In this context it is either mandatory for clinicians focusing on the different treatment options and on probable side effects of each molecules. It is well acquired that among elderly within same age group and strain, the outcome will differ according to each patient's frailty. Moreover, old and frail people are particularly exposed to a double risk: the first one is the age-related mortality and the second one the susceptibility (also age related too) to side effects. Aim of our paper is reporting our experience in reducing toxicity with a constant action of scientific update and subsequent modification in clinical management protocols. Main focus was on frail patients and cardiologic risk-related to hydroxychloroquine.

### Introduction

A novel coronavirus, recently named as SARS-CoV-2 is the responsible of the current outbreak of COVID-19 disease.<sup>1</sup> Since the beginning of the epidemic the virus has been characterized by an age-related fatality rate. Pre-existing cardio-vascular diseases (CVD) may be associated with a more severe COVID-19 infection and some studies found that a history of CVD was associated with a nearly five-fold increase in the case fatality rate when compared with

patients without CVD.<sup>2,3</sup> In addition, the cardiovascular system can be primarily affected by COVID-19, with complications including myocardial injury, myocarditis, acute myocardial infarction, heart failure, dysrhythmias, and venous thromboembolic events. The arrhythmias have been highlighted in about 16% of COVID-19 patients, being more evident in frail elderly patients with comorbidity and polypharmaco-therapy. Moreover, current therapies for COVID-19 can interact with medicines used to manage patients' existing cardiovascular conditions.

HCQ emerged as the key element for treating this disease.<sup>4</sup> This molecule is well known and extensively tested in clinical practice. First developed for malaria treatment and prophylaxis; it then becomes one of the drugs involved in therapy of autoimmune diseases as lupus erythematosus or rheumatoid arthritis for its immunomodulating activity.<sup>5,6</sup> Yao *et al.* at the beginning of the SARS-CoV-2 epidemic proposed HCQ as a treatment option<sup>7</sup> for its antiviral activity and immunosuppressive role in treating hyperinflammation.<sup>4,7</sup>

The main side effects reported in literature and observed in years of clinical practice are cardiac and liver toxicity.<sup>8-10</sup>

Many medications, including drugs prescribed for noncardiac indications, can cause QTc interval prolongation and trigger torsade de pointe (TdP),<sup>11</sup> which may degenerate into ventricular fibrillation and result in sudden cardiac arrest. Numerous risk factors for TdP have been identified.<sup>12</sup> The occurrence of TdP is largely dependent on the presence of underlying risk factors and is an extremely rare occurrence in patients without concomitant risk factors. The Tisdale score<sup>13</sup> was validated as a predictor of TdP in the hospitalized patient population, taking into account the statistically most relevant risk factors (among others age, sex, alterations of electrolyte balance, therapy with diuretics, antecedents of long QT, *etc.*). The elderly is particular prone to adverse effect and negative outcome in stressful conditions. Differences in stress response between individuals with identical chronological age is due to different level of homeostenosis, intended as a reserve capacity to counter high pressure conditions.<sup>14</sup>

A French group reported the efficacy in treating this infection with an association based on azithromycin and HCQ<sup>15</sup> however, macrolides are presenting an addictive effect on QTc elongation when prescribed in association with HCQ.<sup>16,17</sup>

Aim of this report is to focus attention on cardiac HCQ toxicity and reporting our experience.

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### Materials and Methods

We report the evidence emerged by a Longitudinal Prospective Study performed in our hospital in two different days (data collected for seven days from admission): the first one on March 31<sup>st</sup> 2020, and the second one April 22<sup>nd</sup> 2020.

On March 27<sup>th</sup> a new SARS-CoV-2 treatment protocol was applied in our hospital. In order to understand the reasons in the first week of April an intensive training course for nurses and doctors took place (three hours for doctors and four hours for nurses) in order to understand the reasons of protocol change. The training course was organized by the hospital COVID-19 response team.

Study inclusion criteria: all patients admitted to Sanremo Hospital with suspicion of COVID-19 disease with age ranging from 18 years old or above and currently hospitalized at the two time points. Patients that were present at both time points were counted only as members of the first period.

We performed a detailed analysis of patients medical records and for each patient the subsequent data were recorded: i) Date of

admission; ii) Sex; iii) Age; iv) First electrocardiogram (ECG) at admission with QTc calculation; v) Subsequent ECGs with QTc calculation; vi) ECG requested and ECGs effectively evaluated by Consultant cardiologist; vii) Drugs administered.

The statistical analysis was performed using IBM-SPSS 16. The patients' baseline demographic characteristics, QTc length and drugs administered were reported using relevant descriptive statistics (means  $\pm$  standard deviation [SD], median and interquartile range [IQR], or percentage). Kolmogorov-Smirnov tests were used to assess the normal distribution of continuous variables; those with skewed distribution were compared using the Mann-Whitney U test. Categorical variables and continuous variables that were not normally distributed were compared using the  $\chi^2$  test and Kruskal-Wallis test, respectively. Medians across groups were compared using a Median test for 2 independent medians.

The second and third ECG were included only if the patient stayed in hospital more than two and five days respectively.

## Results

Sanremo Hospital is one of three Hospitals belonging to ASL-1 Imperiese Hospital network, west of the Liguria Region in Italy. It offers 250 beds facility including the infectious diseases department (25 beds, 4 consultants and one direc-

tor before the outbreak; 10 consultants nowadays).

On February 28<sup>th</sup> the first patient affected by COVID-19 was admitted, and the Hospital defined a first version of treatment protocol (Table 1). Such protocol was based on the evidence found in the article Gautret *et al.* which suggested that the combination of azithromycin and HCQ had a beneficial role on viral clearance, promoting viral elimination.<sup>15</sup> Furthermore, an important role was assigned at that time to the Protease Inhibitors (PI) use, lopinavir/ritonavir (LPV/r) and darunavir/ritonavir (DRV/r).<sup>18,19</sup>

On March 27<sup>th</sup> the treatment protocol was emended with the withdrawal of azithromycin following the concern raised by several authors.<sup>20</sup> The real efficacy of azithromycin and HCQ combination was questioned and more attention was focused on the risk for arrhythmia.<sup>21</sup> Moreover, in the first half of March 2020 we observed two cases of TdP and one sudden death, which was a further motivation to update the protocol treatment and to extend the monitoring of cardiac toxicity. At the same time the use of PI was restricted to those who presented within the first 7 days from symptoms onset.<sup>22,23</sup> In addition Oseltamivir was stopped for the influenza season ending. So HCQ remained the pivotal molecule in association with heparin,<sup>24</sup> steroids and tocilizumab when requested.<sup>25,26</sup>

In the first period of observation 171 patients were enrolled (55% male) and in the second period 100 new patients were

present in hospital (53% male).

Considering the 271 patients as a whole, 27% were less than 65 years old, 16% were between 65 and 74 and 57% were older than 75 years. The average QTc recorded at the basal ECG at admission is significantly different in the three age groups:  $442 \pm 35$  msec in patients <65 years,  $455 \pm 34$  msec in patients between 65 and 74 and  $458 \pm 38$  msec in patients > 75 years old ( $P=0.01$ ). There were no significant differences between the three age groups as regards the average QTc recorded at the second ECG or the average increase of the QTc duration. Considering the drugs prescription according to the three age groups, there were significant differences in the percentage of patients taking azithromycin (46% vs 59% vs 34%,  $P<0.01$ ), darunavir/ritonavir (38% vs 29% vs 21%,  $P=0.02$ ) and the combination of two or more drugs (73% vs 68% vs 43%,  $P<0.01$ ); no statistical difference for HCQ (94% vs 93% vs 88%,  $P=0.28$ ).

Analyzing patients according to the two different hospitalization periods (March 31<sup>st</sup> and April 21<sup>st</sup>), there is a statistically significant difference regarding the average age:  $71 \pm 15$  years in the first period versus  $75 \pm 16$  years in the second period ( $P=0.01$ ), while there were no differences in sex (males 55% versus 53%).

ECG data split according to the two different periods are summarized in Table 2.

In the first period, basal ECG was present in the clinical record of 85% of patients, 34% of patients had a second ECG and 12%

**Table 1. Drug recommended for covid-19 treatment (March 24<sup>th</sup> 2020).**

Drug	Dosage	Comments
Darunavir/ritonavir	800/100 mg once a day	Use restricted to patients take in charge within 7 days from symptoms onset (27 March)
Azithromycin	500 mg	Not recommended (from 27 March)
Hydroxycloquine	400 mg bid day 1 (loading dose) Followed by 200 mg bid	Maintained in therapy protocol
Ceftaroline	500 mg three times a day	Maintained in therapy protocol
Oseltamivir	75 mg bid. For 5 days	Discontinued from 27 March

**Table 2. Cohort details.**

	First Period (n=170)	Second Period (n=100)	P
First basal ECG			<0.01
Requested and reported	85%	97%	
Requested but not reported	0.6%	3%	
Not requested	14%	0%	
Second ECG			0.01
Requested and reported	34%	77%	
Requested but not reported	15%	5%	
Not requested	51%	18%	

had a third one. In the second period, basal ECG at the time of admission was present in 97% of the patients and a second and a third ECG was present respectively in 77% and 53% of cases ( $P=0.01$ ).

There were no significant differences between the two periods (before and after the change of protocol) in QTc median duration for the first basal ECG (446 vs 453 msec) nor for the second ECG (453 vs 465 msec). Almost half of the patients (47% in the first period and 54% in the second period) had a basal QT interval greater than 450 milliseconds; this percentage rises respectively to 54% and 67% for the QT interval registered at the second ECG, this difference could be due to chance or to the higher average age of patients in the second periods.

The mean QT tract prolongation was  $14\pm 44$  milliseconds, with no differences between the two period (18 vs 11 msec,  $P=0.38$ ).

Drugs prescriptions split according to the two different periods are summarized in Table 3.

Comparing the first and second periods, the prescription of HCQ has dropped from 94% to 85% ( $P=0.02$ ) and that of azithromycin from 50% to 27% ( $P<0.01$ ), while the prescription of protease inhibitors remained stable at around 27%. There has been a slight increase in the intake of potassium supplements (from 27% to 35%,  $P=0.2$ ).

T61% of patients had two or more COVID-19 molecules at high risk for QTc prolongation (HCQ, azithromycin and ritonavir) while 4% patients were free from COVID19 regimen drugs in the first period; these percentages were respectively 45% and 12% in the second period ( $P<0.01$ ).

Considering all 271 patients, QTc median duration at the second ECG was slightly different between patients taking less or more than two drugs with potential QTc prolongation (454 versus 465 msec,  $P=0.08$ ) and this was more evident period

(450 versus 470 msec,  $p=0.06$ ). We found no differences in mean QTc prolongation according to drugs intake.

After protocol change and personnel training, doctors were more prone to request ECG and nurses were likely to perform them, both at time of admission and control checks. The difference seen before and after training is of statistical significance for ECG at baseline ( $P<0.01$ ) and for second ECG ( $P=0.01$ ).

## Discussion and Conclusions

In hospitalized patients is frequently observed a QTc prolongation. A mild increase in QTc could be observed for a wide variability of causes.<sup>27,28</sup> The median age (71 or 76 yrs) of patients admitted to our department is greater than those described in the Chinese cohort (54 yrs).<sup>26</sup> Age itself is representing a risk for the development of arrhythmias, in fact Rabkin *et al.*<sup>29</sup> observed that *older patients have a greater QTc which potentially makes them more vulnerable to situations and medications that prolong QTc. QTc prolongation could be due to a combination of factors related to aging: myocardial fibrosis or an alteration in the balance between sympathetic and parasympathetic tone, which can alter myocardial repolarization and the duration of the QTc. Moreover, older people are more likely to be already taking many medications at home which can interfere with QT prolongation.* This risk is increasing if different elements are added, for example hypokalemia and drug combinations.<sup>13</sup> The risk is well described in the Tisdale risk chart:<sup>13</sup> according to the chart, age is the main determinant for QTc prolongation. Our teaching sessions/training dramatically increased the number of ECG performed and, at the same time, raised the safety of our patients. In the second period median age was greater and this could be the rea-

son for a longer QTc observed at baseline, but a further element could be the start of use of HCQ in the out of Hospital setting managed by general practitioners. Our data are supporting the efficacy of educational meeting aimed to update the prescription schedules and reduce the clinical risk of patient management. In the second period we observed a drastic reduction in macrolides and levofloxacin use in association with HCQ. Moreover, after the training the attention to potassium blood level was increased as shown by the number of patients assuming potassium supplementation (from 27.4% to 35.4%), in the same period a better selection of patients who require the COVID-19 treatment was done (patients not assuming drugs at risk for QT prolongation raised from 4.1% to 12.7%). This paper showed that our action was crucial in raising awareness to QTc prolongation's issue related to drugs association, especially if drugs act on QT-tract. The main result was an improvement in drug-drug interaction management in a pandemic scenario with extensive use of well-known drugs in new combined treatment schedule. After the specific training for COVID-19 QTc prolongation, 44% (61.5% before) of the patients were presenting two or more drug at risk for QTc prolongation, these molecules are frequently belonging to the elderly people therapy schedule We reported only a slightly difference in QTc median duration at the second ECG between patients taking less or more than two drugs with potential QTc prolongation but Mercurio *et al.* noted that concurrent treatment with HCQ and azithromycin was associated with greater changes in QTc.<sup>30</sup> Currently the use of PIs is restricted to selected cases (within 7 days from symptoms onset) based on the results of two different studies including both molecules darunavir/ritonavir and lopinavir/ritonavir.<sup>22,23</sup>

The already cited paper by Molina is addressing in the same direction.<sup>20</sup>

The role of HCQ is actually under dis-

**Table 3. Drugs prescribed (two periods).**

	First Period (n=170)	Second Period (n=100)	P
Hydroxyclochlorine	94.1%	85%	0.02
Azithromycin	50%	27%	<0.01
Protease Inhibitors	27.6%	26.3%	ns
Potassium supplements	27%	35.4%	0.20
Co-administration of drugs at risk for QT prolongation:			<0.01
0 drug	4.1%	12.1%	
1 drug only	34.3%	43.4%	
2 drugs together	47.3%	39.4%	
3 drugs together	14.2%	5.1%	

discussion from several points of view. At the time of writing this report, the results on HCQ efficacy of only two randomized controlled clinical trials were available. A double-blind controlled trial of 62 patients with COVID-19 pneumonia admitted in hospital showed some effect of HCQ on symptoms and radiologic CT scan features, compared to SOC (antivirals, antibiotics, immunoglobulins and/or steroids).<sup>31</sup> A second controlled trial comparing HCQ to SOC (not specified) in 150 patients with COVID-19 pneumonia admitted to hospital showed no differences in the two groups in viral clearance at 28 days.<sup>32</sup> Unfortunately, these two trials lack in quality, numerosity and transparency (patient selection, no double blind, SOC not well specified). The uncertainty of the efficacy of hydroxychloroquine has led to different approaches in COVID-19 patient management. Our choice was to prescribe HCQ in all COVID patients presenting with severe disease, with or without pneumonia.

Nevertheless, waiting for conclusive data, our choice, at that time, was to prescribe HCQ in all COVID patients with severe disease, performing a careful evaluation weighting PROs and CONS especially when prescribing this molecule to elderly people. More recently, further study confirmed<sup>33</sup> no clear benefit from the use of HCQ, this led the Italian drug agency (AIFA) to withdraw the off-label use of HCQ in covid-19 disease unless in the setting of clinical trials.<sup>34</sup>

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