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Original Article

Cardiac Findings in COVID-19 Patients Treated with HAZDPac

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Abstract

Objective: Hydroxychloroquine paired with Azithromycin, Vitamin C, Vitamin D, and Zinc (HAZDPac), was used as a multidrug therapy method to treat COVID-19 illness and superimposed secondary bacterial pneumonia. Concerns have been raised though about such combinations regarding cardiac QTc interval prolongation and risks of arrhythmias, which we set out to address in this study. ***Design:*** We evaluated cardiac safety in a Phase II Double-Blind Randomized Placebo-Controlled Trial of Combination Therapy to Treat COVID-19 Infections study, conducted by ProgenaBiome. Acutely ill patients with COVID-19 had QTc intervals recorded in an outpatient setting utilizing a continuously worn EKG monitor for the duration of the 10 days treatment. QTc intervals were normally distributed. Two-sample t-tests were used to measure any significant differences in QTc intervals between treatment and placebo groups. ***Results:*** Between June 2020 and June 2021, 118 COVID-19 patients were recruited and signed informed consent, of which 83 were enrolled for a Double-Blind Randomized Placebo-Controlled Trial. Of the 83, 52 patients were randomly assigned to receive HAZDPac treatment, and 31 patients to receive placebo. Overall, and in stratified analysis by gender, maximum QTc values of patients in the treatment arm were normal and no differences were observed when compared to maximum QTc values from patients in the placebo arm ($p \geq 0.15$). There were no adverse events related to HAZDPac treatment. ***Conclusion:*** We found that the outpatient treatment of COVID-19 patients with HAZDPac which includes Hydroxychloroquine and Azithromycin, was not associated with prolongation of QTc compared to placebo and QTc remained within normal range.

Keywords: ***COVID-19, hydroxychloroquine, azithromycin, QTc interval, safety.***

Introduction

SARS-CoV-2, or severe acute respiratory syndrome coronavirus 2 is a virus that causes a disease called the coronavirus disease 19 (COVID-19). COVID-19 is a respiratory disease that can be transmitted from humans to humans through suspended droplets dispersed from a sick individual's cough, sneeze, or speech [1,2]. Surface contact transmission rates are extremely low [3]. The SARS-CoV-2 was first identified from a lab in Wuhan, China and spread at an unprecedented rate throughout the world, causing those infected to have flu-like symptoms such as fever, coughing, shortness of breath, loss of taste and smell, headache, and muscle pain as well as gastrointestinal problems (GI symptoms) about 2 to 14 days after exposure, with incubation periods varying from case to case. Prolonged sickness and weaker patients develop severe illness such as pneumonia, respiratory distress, and death.

Hydroxychloroquine is an FDA approved antimalarial drug, originally used to treat acute malaria cases [4]. Hydroxychloroquine was among the first treatments available and tested for COVID-19, however, it did raise concerns among the medical community for its potential risks on cardiac rhythm [5]. There have been several controversial issues regarding treatment with Hydroxychloroquine published by the FDA, announcing that Hydroxychloroquine prolongs the QTc intervals of patients over time during treatment, causing Torsade de Pointes (polymorphic ventricular tachycardia) and other cardiac problems [6-9]. We seek to determine whether studies based in the hospital vs. ambulatory studies, where patients are treated while at home, lead to differing results in the effort to treat COVID-19, and most importantly, whether Hydroxychloroquine is associated with heart irregularities as evaluated by QTc intervals measurements.

Methods

Study Subjects and Study Design

The patients provided informed consent and the study was approved by Salus IRB protocol #20071. The CONSORT flow diagram is shown in **Figure 1**. Between June 2020 to June 2021, 118 COVID-19 patients were approached, of which 83 were recruited for a

Double-Blind Randomized Placebo-Controlled Trial of Quintuple Therapy, NCT04334512. The 83 included subjects were stratified for the double-blind placebo-controlled clinical trial, arm 1 and arm 2 groups: 52 patients were randomly assigned to receive HAZDPac treatment, and 31 patients to receive placebo. We kept the treatment blinded to ensure validity of results and data. All subjects in the clinical trial were treated with either HAZDPac or placebo. All subjects and patients wore continuously recording Infobionic MoMe Kardia EKG devices for the duration of the 10-day treatment. The MoMe Kardia II is a 2-channel recording device that records and displays up to 6 leads of ECG tracings - Lead I, II, II, aVL, aVR, aVF. Advantages of using this device include the small size of this wireless device and the computational power available through cloud computing. For this study we used the lead that was the cleanest/clearest to measure correctly - primarily Lead I. This study was conducted by ProgenaBiome's primary investigator Sabine Hazan, MD and Dr. Alon Steinberg MD and began March 19, 2020, in the very midst of the first wave of the pandemic.

The HAZDPac trial spearheaded studies on the usage of hydroxychloroquine in combination with Azithromycin, vitamin C, vitamin D, and zinc to treat COVID-19 ambulatory, rather than hospitalized patients. Inclusion criteria included being male or female 18 years of age and older, signed informed consent electronically via the EDC, demonstrating that they understood the procedures required for the study and the purpose of the study. Subjects agreed to practice at least one highly effective method of birth control for the duration of the study. This included condoms with spermicide, oral birth control pills, contraceptive implants, intra- uterine devices, or diaphragms. Subjects not of reproductive potential were exempted (e.g., post- menopausal, surgically sterilized). Subjects had a certain diagnosis of COVID-19 by RT-PCR. We excluded subjects that refused to provide informed consent, were pregnant or breastfeeding women, have had diarrhea prior to infection or obtained a negative test for COVID-19 by RT-PCR at screening. Subjects that had any comorbidities which, in the opinion of the investigator, constitute health risk for the subject were also excluded. For example, subjects with any contraindications for treatment with hydroxychloroquine, or who were hypoglycemic, had a known G6PD deficiency, porphyria, anemia, neutropenia, alcoholism, myasthenia gravis, skeletal muscle disorder, maculopathy, changes in visual field, liver disease, psoriasis, history of QT interval >500msec, history of Torsade de Pointes, anemia from pyruvate kinase, G6PD deficiencies, abnormal EKG with QT prolongation acquired or from birth, allergies to 4-Aminoquinolines, history of jaundice or high fevers prior to developing COVID-19, treatment with any contradictory medications and drugs that affects the QT interval, including for Long QT syndrome type 13 (LQT13), or treatment with any anti-epileptics. Subjects were assigned a unique eight-digit identification number. Only personnel on the delegation log had access to study documents. These documents were stored in password-protected computers, and physical documents were stored in secured research facilities per their SOPs.

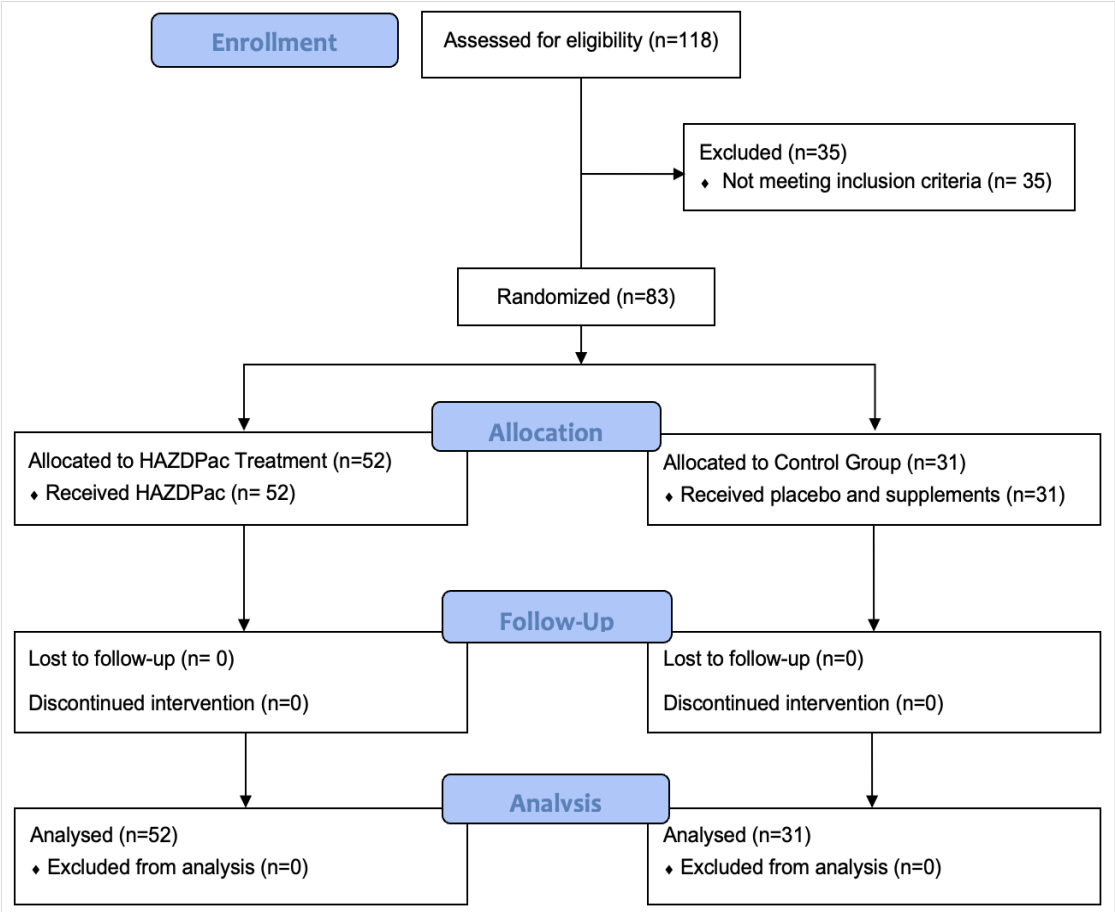

Figure 1. CONSORT Flow Diagram

Treatment Design

Each subject admitted into the study provided informed consent to participate in the study and agreed for publication of the research results. Medical information such as: prior and concomitant medications (including over-the-counter medications and supplements), past medical history, family medical history, as well as demographic information was obtained from each patient and recorded. SARS-CoV-2 infection was confirmed by a nasal or oral swab test, and each subject was given a daily patient diary to record extensive observations and symptoms. Subjects were randomized into two arms, Arm 1, and Arm 2. Arm 1 was given medications prescribed for Quintuple Therapy: Hydroxychloroquine 200 MG

BID for 10 days, Azithromycin 500 mg on day 1, 250 mg day 2-5, Vitamin C 3000 mg for 10 days, then 1500 mg for 20 days, Vitamin D 3000 IU for 10 days, then 1500 IU for 20 days, and zinc 50 mg for 10 days, then 25 mg for 20 days. Arm 2 was given placebos and supplements (to ensure nutritional parity): Placebo for Hydroxychloroquine BID for 10 days, Placebo for Azithromycin to be taken 2 on Day 1, then 1 on Days 2-5, Vitamin C 3000 mg for 10 days, then 1500 mg for 20 days, Vitamin D 3000 IU for 10 days, then 1500 IU for 20 days, and zinc 50 mg for 10 days, then 25 mg for 20 days.

Patient Monitoring included EKG response, oxygen saturation, and vital signs. All patients were given home EKG recording devices, pulse oximeters, thermometer, urine pregnancy tests (if applicable), and all patients had to follow self-quarantine guidelines per CDC recommendations. Each patient was instructed to monitor their EKG response, oxygen saturation, and vital signs each day and record each observation in the daily diaries given to them at the beginning of the study. Subjects were called on the first day, third day, fifth day, seventh day, tenth day, fourteenth day to check in on patient vitals and symptoms. Afterwards, each patient was called or brought into the clinic (after a negative COVID test result was obtained) and checked in once per month for the next three months during the follow up period.

COVID-19 Sample Collection: Nasal swabs were collected according to CDC protocol with synthetic fiber swabs with plastic shafts that were inserted into the patients' nostrils parallel to the palate. Oropharyngeal swabs were collected according to CDC protocol with synthetic fiber swabs with plastic shafts that were inserted into the mouth and touched the area near the tonsils five times. Samples for COVID-19 testing were collected by the Subject using synthetic swabs with plastic shafts. Oropharyngeal swabs were collected and immediately placed into a sterile vial with 2-3 mL of viral transport media. These were placed into biohazard bags, boxed up, the box sterilized, and picked up for shipment to the central laboratory. Samples were tested by RT-PCR, and then were stored by the Cole Laboratories central lab for potential future testing and analysis.

Hospitalization Protocol: Should a subject's symptoms worsen, they would have been referred to their CP for further evaluation and possible subject hospitalization.

QTc Analysis: The daily QTc intervals from each patient wearing holters were recorded and inputted into a chart to investigate and look for any significant deviation over the limit of 460 QTc, indicating a prolonged QTc interval. Other cardiac anomalies were searched for and charted accordingly. Normal distribution was visually assessed before performing parametric analysis. Two-sample t-tests were used to measure any significant differences in QTc intervals between treatment and placebo groups. A p-value of < 0.05 was considered statistically significant.

Results

Study Participants

Table 1 shows the characteristics of the study participants. In the Treatment arm (n=52), subjects had a mean age of 49 years (SEM, range: 15.92, 18-82), 52% were females, 69% were of white race/ethnicity, 17% Hispanic, 6% Asian, 4% Native American, and 4% of unknown race/ethnicity. The most common comorbidity in this group was cardiovascular conditions (n=9, 17%), while four patients suffered of either type 2 diabetes mellitus, COPD, chronic kidney disease, or obesity and one was immunocompromised, for a total of 75% without any co-morbidity, 23% with 1 co-morbidity, and 2% with two comorbidities.

In the Placebo arm (n=31), subjects' mean age was 49 years old (SEM, range: 12.65, 31-74), 52% were females, 68% were of white race/ethnicity, 3% black, 26% Hispanic, and 3% of unknown race/ethnicity. 32% had a heart condition (n=10), 3% (n=1) had Type II Diabetes Mellitus, 3% (n=1) had COPD, 3% (n=1) were obese, and 3% (n=1) were immunocompromised, for a total of 52% without any co-morbidity, 42% reporting 1 co-morbidity, and 6% reporting 2 co-morbidities (**Table 1**).

QTcs Values among the Double-Blind Randomized Placebo-Controlled Trial Participants

In Table 2, the QTc values for participants in each Arm are shown. The mean Min QTc value, 353 ms (SD: 23) in the HAZDPac treated group was within the normal range, though statistically significantly higher than that of the placebo group, mean (SD): 341 ms (23), p=0.03. The mean Max QTc value of 430 ms (SD: 33) in the treated group was also within normal range and comparable to the one measured in the placebo group, mean Max QTc value 421 ms (SD: 33), p=0.246.

When analyses were stratified by gender, all results were statistically not significant. Table 2 shows that females in the treatment arm had Min and Max QTc values that were similar to those of women in the placebo arm, 352 ms (SD: 20) vs. 338 ms (SD:26), p=0.086; 437 ms (SD:32) vs. 425 ms (SD:34), p=0.261, respectively. For males, Min and Max QTc values in the treatment arm were also similar to those in the placebo arm, 353 ms (SD: 27) vs. 344 ms (SD:19), p=0.203; 423 ms (SD:33) vs. 418 (SD:33), p=0.636, respectively. **Figure 2** shows an example QTc interval before and after 9 days of HAZDPac treatment from a selected study participant.

None of the COVID-19 patients treated with HAZDPac had severe adverse events nor died, proving that this therapy may be safe and effective.

Table 1: Study Participant Characteristics

	Arm 1: Hydroxychloroquine n=52	**Arm 2: Placebo n=31**
Age (mean, SEM, range)	48.96, 15.92, 18-82	48.94, 12.65, 31-74
Male (n, %)	25 (48.08%)	15 (48.39%)
Female (n, %)	27 (51.92%)	16 (51.61%)
Race (n, %)	**# Of Subjects (%)**	**# Of Subjects (%)**
White	36 (69.23%)	21 (67.74%)
Black	0 (0%)	1 (3.22%)
Asian	3 (5.77%)	0 (0.00%)
Hispanic	9 (17.31%)	8 (25.81%)
Native American	2 (3.85%)	0 (0%)
Unknown	2 (3.85%)	1 (3.22%)

Comorbidity	# Of Subjects (%)	# Of Subjects (%)
Type 2 Diabetes Mellitus	1 (1.92%)	1 (3.22%)
Heart or Cardiovascular	9 (17.31%)	10 (32.26%)
COPD	1 (1.92%)	1 (3.22%)
Obesity (BMI ≥ 25)	1 (1.89%)	1 (3.22%)
Chronic Kidney Disease	1 (1.92%)	0 (0.00%)
Immunocompromised	1 (1.92%)	1 (3.22%)
# Of Comorbidities	**# Of Subjects (%)**	**# Of Subjects (%)**
0	39 (75%)	16 (51.61%)
1	12 (23.08%)	13 (41.94%)
2	1 (1.92%)	2 (6.45%)

Table 2. QTc Value Statistical Comparison for HCQ Patients and Arm 2

	Arm 1: Hydroxychloroquine	Arm 2: Placebo	p-value
All	**N=52**	**N=31**	
Min QTc (ms) Mean (SD)	352.692 (23.210)	341.129 (22.829)	**0.030**
Max QTc (ms) Mean (SD)	430.289 (33.113)	421.452 (33.372)	0.246
Females	**N=27**	**N=16**	
Lower QTc (ms) Mean (SD)	352.037 (20.156)	338.438 (26.184)	0.0858
Higher QTc (ms) Mean (SD)	437.222 (32.086)	425 (34.737)	0.261
Males	**N=25**	**N=15**	
Lower QTc (ms) Mean (SD)	353.4 (26.525)	344 (19.105)	0.203
Higher QTc (ms) Mean (SD)	422.8 (33.200)	417.667 (32.616)	0.636

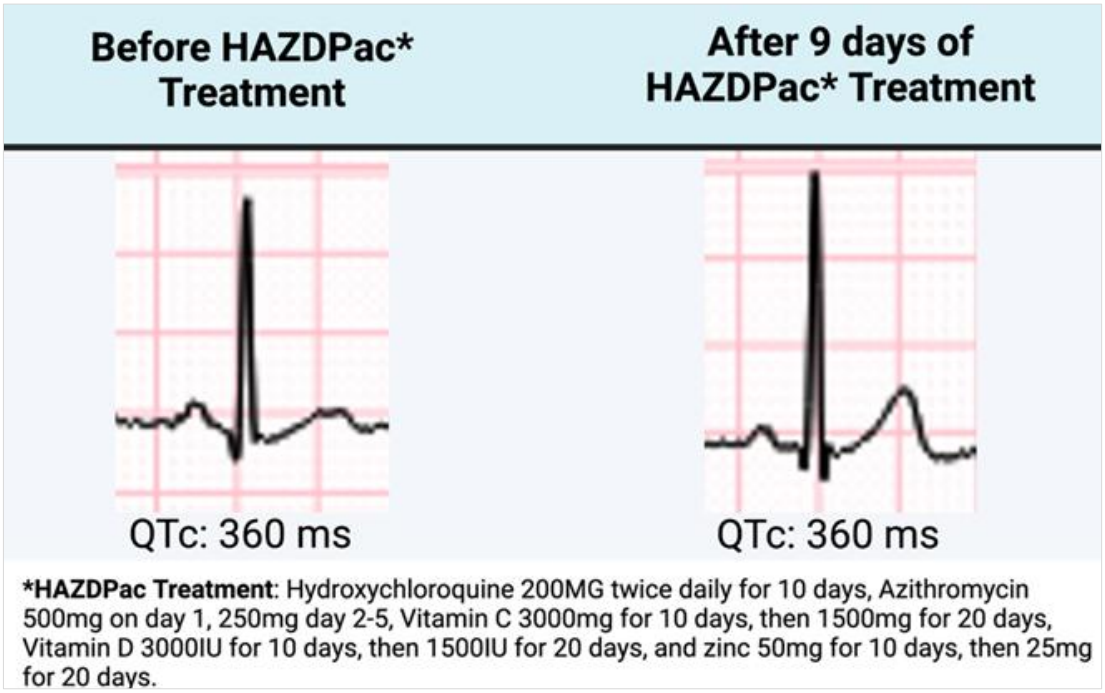

Figure 2: Example QTc interval derived from a study participant before and after 9 days of HAZDPac treatment

Discussion

We found that hydroxychloroquine in conjunction with other drugs used in standard-of-care for ambulatory acute COVID-19 did not impact the QTc interval measured in an assiduous continuous monitoring environment. Hydroxychloroquine has been a controversial drug due to the speculation that either alone or paired with azithromycin taken orally leads to a prolonged QTc interval and Torsade de Pointes, particularly in an inpatient hospital setting [10-13].

Yet, in this outpatient setting study conducted by ProgenaBiome, a private research clinic located in Ventura, California, such cardiac findings of patients treated with Hydroxychloroquine, paired with Azithromycin, Vitamin C, Vitamin D, and Zinc (HAZDPac) did not reflect previous concerns. The mean maximum QTc value found in the data we gathered from treated patients' continuously worn EKG monitor was 437 ms (SD=32), which falls into the normal range for both males and females, QTc normal range for males is 350-450 ms, and for females is 360-460 ms [14].

The present results agree with similar data reported in larger cohort studies. For example, a multi-center study of eight secondary and tertiary care hospitals of the Abu Dhabi Health Services Company (SEHA), United Arab Emirates, that included 2,014 patients consecutively admitted with PCR-confirmed SARS-CoV-2 infection between March 1 2020 and June 1 2020, found that the incidence of severe QTc prolongation with hydroxychloroquine treatment was low and not associated with ventricular arrhythmia[15].

A large study among 965 hospitalized patients at Columbia University Irving Medical Center investigated whether infection with COVID-19 was associated with prolonged QT intervals on electrocardiograms. They found that COVID-19 infection was independently associated with significant mean QTc prolongation at days 5 and 2 of hospitalization compared with day 0 and compared with patients without COVID-19 [16]. They also found that 19 of 255 patients (7.5%) with COVID-19 receiving hydroxychloroquine with azithromycin had QTc of at least 500 ms compared with patients without COVID-19, although this difference was not statistically significant (p= 0.49) [16]. In our study, all outpatients had COVID-19 infection and the QTcs of patients receiving HAZDPac were not statistically significant different from the QTcs of the patients in the placebo arm. In addition, none of the HAZDPac treated patients had severe adverse events nor died.

In a study by Lagier et al, 2022, among 2,111 hospitalized COVID-19 patients in France, the treatment with Hydroxychloroquine/Azithromycin was associated with lower mortality [17]. This observation was further validated in an even larger analysis of a database of 30,423 COVID-19 patients [18]. Moreover, in an analysis of 26 trials comprising 10,012 patients and that included two of the largest trials on Hydroxychloroquine to treat COVID-19, RECOVERY [19] and WHO SOLIDARITY [20], it was reported that the average mortality rate was 10.3% in inpatient trials and 0.08% in outpatient trials [21]. However, the study concludes that overall, treatment with hydroxychloroquine was associated with increased mortality in COVID-19 patients. More importantly, they admitted that *findings have unclear generalizability to outpatients*, which our study significantly explored. The RECOVERY trial claims that Hydroxychloroquine was associated with a 0.4% increased risk of death from cardiac events in hospitalized patients, although this association was not statistically significant [19]. A follow-up systematic review including 44 worldwide cohort studies, recently published by Pradelle *at al.*, 2024, estimated that the in-hospital mortality of COVID-19 patients treated with Hydroxychloroquine was 16,990 patients, however they failed to take into account the dosage and when the treatment began, i.e. whether late into the hospitalization phase [22].

This brings us to discuss two major points that are not well addressed in the meta-analysis of hydroxychloroquine clinical trials conducted worldwide [21,22]. One is the dose of hydroxychloroquine prescribed to patients, and another is how early in the treatment hydroxychloroquine was given, including to patients with severe COVID-19 already hospitalized, when hydroxychloroquine may not be as effective. In the RECOVERY trial, patients received an initial 800 mg dose of hydroxychloroquine, followed by 400 mg every 12 hours for up to 9 days or until discharge [19]. In the WHO SOLIDARITY trial, patients received 800 mg of hydroxychloroquine at hour 0, another 800 mg at hour 6, and then 400 mg twice daily starting at hour 12 for 10 days [20]. Both trials included hospitalized COVID-19 patients that were given relatively high doses of hydroxychloroquine, which may have influenced the observed mortality outcomes associated with hydroxychloroquine. Our study shows that early outpatient administration of HAZDPac, which included 200 mg Hydroxychloroquine twice a day for 10 days, was safe in treating COVID-19 with no adverse effects, no prolonged QTc and no cardiac arrythmias or events. A recent review article on cardiac biomarkers studies among COVID-19 patients highlights the importance of identifying early the most serious patients in order to optimize their outcomes. These biomarkers should be considered in patient settings where there are doubts about the safety of Hydroxychloroquine among patients with a history of heart disease [23].

Finally, in contrast to the data that the FDA published, there have been studies on treatment of patients with COVID-19 receiving lower doses of what the FDA cited, paired with “other hERG-blocking drugs such as azithromycin, or lopinavar/ritonavir should be assessed” [24]. hERG (or human-ether-a-go-go-related-genes) potassium channel blocking drugs have been investigated to lead to prolonged and abnormal QTc interval and Torsade de Pointes [25].

The limitations of our study include the small sample size, with the majority being White participants, and that the analyses were not adjusted for co-morbidities nor COVID-19 severity. Another limitation was the limited sample size for stratified analysis by gender for which statistical power may have been limited, which could mean the null association found could be due to a type II error or false negative results. However, this study included a control arm, which many studies did not have [8-13,15]. Advantages of using the Infobionic MoMe Kardia II device included the small size of this wireless device and the computational power available through cloud computing. The Infobionic MoMe Kardia II device captures all the different data that the three existing arrhythmia diagnostic tools use, thus no need to use different devices. Therefore, outpatients in this study had continuous telemetry monitoring, as done in the hospital, which gives strength to the results. Indeed, the QTc data clearly showed that no cardiac complications were observed with early treatment of hydroxychloroquine in an outpatient setting. These findings should be validated in larger future studies.

In conclusion, our Phase II Double-Blind Randomized Placebo-Controlled Trial of Combination Therapy to Treat COVID-19 Infections (HAZDPac) showed that there was no significant prolongation of QTc and QTc remained normal. Thus, Hydroxychloroquine was not associated with significant prolongation of QTc compared to placebo and QTc remained within normal range.

Declarations

Ethics approval and consent to participate

This study involves human participants, and the study protocol was reviewed and approved by The Salus Institutional Review Board, Protocol #20071 and registered at Clinicaltrials.gov, Identifier NCT04334512. Participants gave informed consent to participate in the study before taking part.

Consent for publication

All authors gave consent for publication. Participants gave written informed consent for their unidentified personal or clinical details along with any images to be published in this study.

Availability of data and material

Data are available upon reasonable request.

Funding Statement

N/A

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Disclosures

Dr Hazan is the CEO of Progenabiome, LLC and owns the Microbiome Research Foundation. Dr. McCullough owns the McCullough Foundation.

Intellectual property information

US11166971B2 patent to Dr. Sabine Hazan for Methods of treating COVID-19 infection.

Data availability statement

All data generated or analysed during this study are included in this published article, the datasets analysed during the current study are available from the corresponding author on reasonable request.

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