



A call to caution when hydroxychloroquine is given to elderly patients with COVID-19

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ABSTRACT

Introduction: Use of hydroxychloroquine in patients with coronavirus disease 2019 (COVID-19) was widespread and uncontrolled until recently. Patients vulnerable to severe COVID-19 are at risk of hydroxychloroquine interactions with co-morbidities and co-medications contributing to detrimental, including fatal, adverse treatment effects.

Methods: A retrospective survey was undertaken of health conditions and co-medications of patients with COVID-19 who were pre-screened for enrolment in a randomized, double-blind, placebo-controlled hydroxychloroquine multi-centre trial.

Results: The survey involved 305 patients [median age 71 (interquartile range 59–81) years]. The majority of patients ($n = 279$, 92%) considered for inclusion in the clinical trial were not eligible, mainly due to safety concerns caused by health conditions or co-medications. The most common were QT-prolonging drugs ($n = 188$, 62%) and haematologic/haemato-oncologic diseases ($n = 39$, 13%) which prohibited the administration of hydroxychloroquine. In addition, 165 (54%) patients had health conditions and 167 (55%) patients were on co-medications that did not prohibit the use of hydroxychloroquine but had a risk of adverse interactions with hydroxychloroquine. The most common were diabetes ($n = 86$, 28%), renal insufficiency ($n = 69$, 23%) and heart failure ($n = 58$, 19%).

Conclusion: The majority of hospitalized patients with COVID-19 had health conditions or took co-medications precluding safe treatment with hydroxychloroquine. Therefore, hydroxychloroquine should be administered with extreme caution in elderly patients with COVID-19, and only in clinical trials.

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Introduction

The coronavirus disease (COVID-19) pandemic initiated an urgent search for safe, effective treatments. Repurposing approved drugs for the treatment of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection can save considerable effort, time and costs (Krishna et al., 2020). These drugs must be suitable for use in elderly patients and those with underlying health conditions as these groups are at particular risk of severe disease and complications.

One such drug is hydroxychloroquine (HCQ), a less toxic and more effective derivative of chloroquine (CQ) (Liu et al., 2020; Yao et al., 2020). With many years of clinical experience, a well-understood safety record, low cost and promising antiviral in-vitro activity, HCQ seemed to be an ideal candidate to manage the COVID-19 pandemic. As such, it was added to the national treatment recommendations in China, the USA (Gao and Hu, 2020; Lei et al., 2020), France, India, Brazil and other countries. On 1 April 2020, the European Medicines Agency stated that HCQ should only be used in clinical trials or emergency use programmes (Lei et al., 2020). Until recently, the majority of hospitalized patients with COVID-19 have been treated with HCQ, including in the European Union. HCQ has a narrow therapeutic range. Unfortunately, it has been given in varying doses, sometimes reaching dangerous cumulative levels. Its assumed positive effect often led to a very optimistic risk–benefit assessment, even in the presence of underlying health conditions or concomitant medications. Concerns about the efficacy and safety of HCQ were soon raised (Rosenke et al., 2020). Unfavourable clinical courses,

increased adverse effects and higher mortality rates were discussed in public media, mainly due to the known life-threatening side effects of CQ and HCQ (Borba et al., 2020). Most of these side effects (e.g. cardiac arrhythmias) and unfavourable outcomes occurred in patients with severe COVID-19 and underlying health conditions (Magagnoli et al., 2020; Rosenberg et al., 2020), and could have been avoided by more conservative assessment of potential risks with regard to co-morbidities and concomitant medications.

While conducting a multi-centre placebo-controlled trial with HCQ in hospitalized patients with COVID-19, the authors encountered many obstacles to patient recruitment. Most patients could not be enrolled in the trial due to co-medications or underlying health conditions interfering with safe use of HCQ.

As such, the authors decided to undertake a retrospective survey to determine, in a representative population of hospitalized patients with COVID-19, the fraction of patients who cannot be safely treated with HCQ according to the summary of medicinal product characteristics (SMPC) (Sanofi, 2019). The population consisted mainly of elderly patients with pre-existing medical conditions (a group at high risk of severe COVID-19).

Methods

A retrospective evaluation was undertaken of the medical records of hospitalized patients screened for eligibility for participation in a randomized, double-blind, HCQ placebo-controlled multi-centre phase II trial (COV-HCQ trial, EudraCT no. 2020-001224-33) to assess the safety and efficacy of HCQ

Table 1

Trial exclusion criteria and medical conditions and concomitant medications unfavourable for use of hydroxychloroquine (HCQ).

	n	(%)
Patients with COVID-19 considered for inclusion in COV-HCQ study (total)	305	(100)
Patients did not consent	27	(8.9)
Patients included in COV-HCQ study	26	(8.5)
Patients excluded due to health conditions and co-medications	252	(82.6)
Exclusion of patients due the following criteria: ^a		
Intake of QT-prolonging drugs ^b	188	
Treatment in intensive care unit	47	
Haemato-oncologic/haematologic diseases	39	
Dementia/cognitive impairment	34	
Prolonged QT interval ^c	13	
Retinopathy	7	
Intake of experimental COVID-19 treatment	7	
Intake of HCQ	5	
Acute myocardial infarction	2	
Percutaneous endoscopic gastrostomy	2	
Bradyarrhythmia	1	
Severe cardiac failure	1	
Delirium	1	
Low weight	1	
Myasthenia gravis	1	
Pregnancy	1	
Additional underlying medical conditions unfavourable for HCQ intake: ^d		
Diabetes	86	
Renal insufficiency	69	
Heart failure	58	
Severe cardiac disorder	39	
Epilepsy	10	
Hepatic impairment	3	
Psoriasis	2	
Additional concomitant medication: ^d		
Patients with concomitant medications interacting with HCQ	167	
Cumulative number of concomitant medications in 167 patients	236	

COVID-19, coronavirus disease 2019.

^a Patients presented with at least one exclusion criterion.

^b Cumulative number of QT-prolonging drugs in 188 patients: 375.

^c Electrocardiogram and QT were not available for all patients.

^d Patients presented with further medical conditions and/or took concomitant medications that warrant increased attention and a careful risk–benefit assessment if HCQ treatment is considered according to the summary of medicinal product characteristics.

treatment in hospitalized patients with COVID-19. In brief, hospitalized adults with a positive SARS-CoV-2 polymerase chain reaction (PCR) result were enrolled and received once-daily HCQ for 7 days (800 mg on day 1, 600 mg/day on days 2–7). These patients were followed-up until viral clearance and for safety investigations. The study was conducted in Germany at the University Hospitals of Tübingen and Hamburg, and local hospitals in Balingen, Reutlingen and Stuttgart. The COV-HCQ trial and the retrospective evaluation of medical reports were approved by the responsible ethics committees in Tübingen, Stuttgart and Hamburg. The clinical trial was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained for trial participation, and only de-identified data were collected for the retrospective analysis.

After the retrospective data evaluation was approved by the local ethics committees, hospital electronic health records were searched and de-identified patient data were collected for hospital stays from 27 March to 28 May 2020. The inclusion criteria for the retrospective evaluation were: adult, hospitalized patients and PCR-confirmed SARS-CoV-2 infection via nasopharyngeal swab. The following variables were analysed: age, date of SARS-CoV-2-positive nasopharyngeal swab, concomitant medication, and underlying health conditions. Safety margins for the use of HCQ in the COV-HCQ trial were pre-defined in the trial exclusion criteria, adhering to the SMPC (Sanofi, 2019), and the recommendations of the Federal Institute for Drugs and Medical Devices and local ethics committees. In addition, concomitant medications were checked for interactions with HCQ using crediblemeds.org, Medscape drug interaction checker, Liverpool COVID-19 Drug Interaction and UptoDate. Data analysis was performed using JMP (SAS). Wilcoxon test and Kruskal–Wallis test were used for numeric and non-parametric data, respectively.

Results

In total, 305 hospitalized patients with COVID-19 were screened for eligibility for enrolment in the COV-HCQ trial, and formed part of this retrospective evaluation. Among the patients, 178 (58%) were males. Their median age was 71 [interquartile range (IQR) 59–81] years. Female patients [median age 73 (IQR 61–83) years] were older than male patients [median age 69 (IQR 58–80) years; $P = 0.046$].

Of the screened patients, 252 (83%) could not be enrolled in the COV-HCQ trial due to safety concerns caused by concomitant medications or various health conditions (Table 1), and 27 (9%) of screened patients did not give informed consent to participate in the trial.

The most common reason for exclusion ($n = 188$, 62%) was intake of drugs that could prolong the QT interval and cause cardiac abnormalities, ranging from concomitant intake of one to six QT-prolonging drugs. Overall, 375 QT-prolonging drug prescriptions were found as co-medications in this cohort. Other common reasons for exclusion were intensive care unit treatment ($n = 47$, 15%), haematologic or haemato-oncologic diseases ($n = 39$, 13%) and dementia/cognitive impairment ($n = 34$, 11%) (Table 1). Five patients were already receiving HCQ as co-medication.

In addition, 244 (80%) of all patients with COVID-19 had medical conditions and/or were taking medications that are not strictly contraindicated but could be unfavourably affected by HCQ. Interfering health conditions were identified 267 times in 165 (54%) patients. The most common were diabetes ($n = 86$, 28%), renal insufficiency ($n = 69$, 23%) and heart failure ($n = 58$, 19%). Intake of concomitant medications other than QT-prolonging drugs that can interact with HCQ was found in 167 (55%) patients. The number of trial exclusion criteria, and

interfering health conditions or co-medications increased with age ($P < 0.001$). In total, 279 (92%) of the screened patients were not eligible for inclusion in the COV-HCQ trial, mainly due to safety concerns caused by health conditions or concomitant medications.

Discussion

This evaluation of medical conditions and co-medications that preclude safe use of HCQ focused on hospitalized patients with COVID-19 in Germany. The majority were elderly patients with multiple underlying health conditions. Dementia and haematologic/haemato-oncological diseases were common co-morbidities that did not allow trial inclusion. Other co-morbidities such as diabetes, renal insufficiency and heart failure were additional reasons to avoid HCQ treatment. These diseases are not only linked to the age of this cohort – which itself poses a risk of severe COVID-19 – but are also associated with higher risk of an unfavourable clinical course of COVID-19 (National Center for Immunization and Respiratory Diseases, 2020)

Co-medications are another obstacle to safe use of HCQ in elderly patients with COVID-19. Some adverse effects may not be clinically significant but can, rarely, have severe consequences. When HCQ administration is considered, particular attention should be given to prescribed concomitant QT-prolonging drugs. Most of the screened patients took at least one QT-prolonging drug, and half of them took two or more. Cardiac arrhythmias due to QT prolongation and ventricular tachycardia in patients treated with CQ led to stopping a trial in Brazil (Borba et al., 2020). When national treatment recommendations suggested HCQ for the treatment of COVID-19 during the first pandemic wave, high numbers of patients were treated with HCQ on a regular basis, and screening for these known side effects was not always applied.

Data in a recent meta-analysis including 28 randomized controlled trials investigating HCQ or CQ as treatment for COVID-19 showed a combined odds ratio (OR) for all-cause mortality of 1.11 [95% confidence interval (CI) 1.02–1.20] in the HCQ-treated patients (Axfors et al., 2021), which indicates a negative effect of HCQ in the study population. The results were mainly driven by the RECOVERY trial and the World Health Organization's SOLIDARITY trial, which contributed 47% and 19% of the analysed patients and had ORs for mortality of 1.11 (95% CI 0.96–1.27) and 1.21 (95% CI 0.89–1.63), respectively. In both trials, very high doses of HCQ were used (800 mg at hours 0 and 6, 400 mg at hour 12 followed by 400 mg every 12 hours for 9 days in RECOVERY or for 10 days in SOLIDARITY), comparable with twice the maximum recommended daily dose and reaching levels of acute intoxication according to the SMPC (RECOVERY Collaborative Group et al., 2020; Repurposed Antiviral Drugs for Covid-19 – Interim WHO Solidarity Trial Results, 2021). Both trials included patients with co-morbidities comparable with those in the COV-HCQ trial. Recruitment rates of 67% (RECOVERY) and 99% (SOLIDARITY) were much higher compared with the COV-HCQ trial (8%). Respectively, mortality rates were 26% and 12% compared with 3% in the COV-HCQ trial (RECOVERY Collaborative Group et al., 2020; Repurposed Antiviral Drugs for Covid-19 – Interim WHO Solidarity Trial Results, 2021). In the meta-analysis, a subgroup of mainly still unpublished, smaller, well-conducted placebo-controlled trials showed a trend towards a benefit for HCQ-treated patients with lower mortality (OR 0.88, 95% CI 0.55–1.41) (Axfors et al., 2021). Careful screening, information and selection of patients for safe use of HCQ resulted into exclusion of 92% of potential study participants in the COV-HCQ trial, in clear contrast to the RECOVERY and SOLIDARITY trials (Table S1, see online supplementary material).

Taken together, uncontrolled and widely applied treatment with HCQ in patients with COVID-19 was predictably more harmful than helpful, particularly in elderly patients. Widespread HCQ administration to elderly patients with COVID-19 is not feasible given the high rate of underlying health conditions and/or concomitant medications. Although the results from randomized, placebo-controlled, double-blinded trials with HCQ in patients with COVID-19 are not yet available, there are increasing indications that HCQ may not be substantially beneficial for these patients. There may be a niche for justified use in well-assessed patients, if randomized controlled trials can demonstrate that HCQ is efficacious and has a beneficial effect in patients with COVID-19. However, the administration of HCQ to virtually all hospitalized patients with COVID-19 is harmful and should be stopped.

Conflict of interest

None declared.

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Ethical approval

The COV-HCQ trial and the retrospective evaluation of medical reports were approved by the responsible ethics committees in Tübingen, Stuttgart and Hamburg. The clinical trial was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained for trial participation and only de-identified data were collected for the retrospective analysis.

Author contributions

Gabor J, Weber S, Sulyok M and Sulyok Z had full access to all of the data in the study; all authors take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design, acquisition, analysis and interpretation of data: all authors.

Drafting and critical revision of the manuscript for important intellectual content: all authors.

Statistical analysis: Gabor J and Weber S.

Administrative, technical and material support: Koehne E, Kreidenweiss A and Köhler C.

Supervision: Kremsner P.

All authors approved the final version of the paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2021.04.009>.

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