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Rational use of chloroquine and hydroxychloroquine in times of COVID-19

Rosa Camila Lucchetta[1]*; Patrícia de Carvalho Mastroianni[1]

[1]Departamento de Fármacos e Medicamentos, Faculdade de Ciências Farmacêuticas, Universidade Estadual Paulista "Júlio de Mesquita Filho" (UNESP), Araraquara, SP, Brasil.

ABSTRACT

Considering the COVID-19 pandemic declared, part of the researchers' efforts has been in studies of repurposing chloroquine (CQ) and hydroxychloroquine (HCQ), cheap medicines that have been used for decades with indication for malaria, rheumatoid arthritis and systemic lupus erythematosus. Chinese and South Korean health officials recommended the use of QC and HCQ for prophylaxis and treatment of COVID-19, encouraging researchers around the world to assess the potential of these medicines as antivirals. To date, results of three clinical trials have been released. Two studies show divergent results for virological clearance, while the third suggests a benefit in terms of radiological and clinical improvement. The three studies have methodological limitations and low overall quality of evidence, in view of the absence of randomization, allocation concealment, blinding patients, health care providers, and outcome assessors, missing data and/or selective reporting of results, as well as probable heterogeneity of patients and treatments, imprecision due to the reduced statistical power of the studies, indirect evidence for patients with severe form of the disease or patients with high severity comorbidities. The irresponsible self-medication of these medicines is of concern both for the potential risk of shortages, as well as for the adverse events and potentially fatal intoxications. Thus, in the USA, Europe and Brazil, regulatory agencies have positioned themselves in an emergency, authorizing the use of CQ and HCQ under medical criteria and/or in the context of clinical trials. In Brazil, to restrict irresponsible self-medication and possible shortages, Anvisa included the drugs in a special control list. Evidence on the efficacy and safety of QC and HCQ remains uncertain, so the results of ongoing studies are needed to adequately guide public policy and clinical practice. Evidence-based health assumptions must be maintained even in times of international emergency due to the risk of having to deal with future complications from the irrational use of these medicines.

Keywords: Evidence-based Practice. Evidence-informed Policy. SARS Virus.

**Corresponding author:* rc.lucch@yahoo.com.br

On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease (COVID-19) pandemic. After almost 30 days, totaling 1.9 million cases and 116,000 deaths worldwide directly attributable to COVID-19 (Dong et al., 2020), there are no a vaccine, drug prophylaxis or effective and safe cure. This scenario has generated pressure on researchers around the world to conduct pre-clinical and clinical studies for rational planning or repurposing of various health technologies for COVID-19. Some of these drug repurposing studies focus on the evaluation of two cheap and old medicines of malaria, systemic lupus erythematosus and rheumatoid arthritis: chloroquine (CQ) and hydroxychloroquine (HCQ).

In vitro studies (Ferner & Aronson, 2020; Wang et al., 2020), the observation of the absence of COVID-19 among Chinese patients with lupus and chronic users of HCQ (Chen et al., 2020b), its promising results, but also controversial against other viruses (Li et al., 2017; Ferner & Aronson 2020), among other evidences, may have contributed to Chinese (Yao et al., 2020) and South Korean (Sung-Sun, 2020) health authorities to recommend the use of CQ and HCQ for prophylaxis and treatment of COVID-19.

The recommendation of CQ and HCQ use has won sympathizers around the world regarding the antiviral potential of these aminoquinolones against the new coronavirus (Cortegiani et al., 2020). However, the mechanism of action or even the in vitro efficacy are not sufficient to prove the effectiveness of these drugs in the general population, requiring the development of clinical studies to answer, among other questions: "CQ or HCQ?" "CQ or HCQ should be associated with other medications?"; "Are prophylaxis or treatment recommended?" "What is the ideal dose in each case and for how long?" "What is the safety profile in the general population and in patients with comorbidities?" and What are the benefits for outpatients or those with moderate or severe COVID-19?

Clinical studies and uncertainties

In order to answer some of these questions, the results of three clinical trials have been released so far (Tables 1 and 2).

Chen et al. (2020a) in an open randomized clinical trial of 30 participants identified absence of difference between HCQ and standard treatment for virological clearance outcome. In this study, the absence of blinding patients, health care providers, as well as uncertainty regarding the

Table 1. Summary of three clinical studies with reported results.

	Chen et al. (2020a)	Gautret et al. (2020)	Chen et al. (2020b)
Publication date	March 6, 2020	March 20, 2020	March 31, 2020
Study design	Randomized open clinical trial	Open non-randomized clinical trial	Randomized clinical trial
Population	Adult hospitalized patients without severe comorbidities (n = 30)	Hospitalized adult patients (n = 42)	Hospitalized patients with mild disease, without severe comorbidities (n = 62)
Intervention	HCQ 400 mg / day for 5 days	HCQ 600 mg / day for 10 days; HCQ 600 mg / day for 10 days + azithromycin (500 mg / day + 250 mg / day for 4 days)	HCQ 400 mg / day for 5 days
Control	Standard treatment (no information)	Standard treatment (no information)	Standard treatment (i.e. oxygen therapy, antiviral agents, antibacterials and immunoglobulin, with or without corticosteroids)
Outcomes	Absence of viral detection in oropharyngeal swab by PCR; Adverse events; Time to negative viral load; Radiological progression; Mortality.	Absence of viral detection in oropharyngeal swab by PCR	Adverse events; Radiological progression; Time for clinical improvement.
Risk of bias	High	High	High

HCQ: hydroxychloroquine; PCR: Polymerase chain reaction.

Table 2. Potential impact of methodological limitations in clinical trials.

Absence of	High risk of
Randomization	Baseline characteristics (e.g. disease severity) influence outcomes
Allocation concealment	Prediction of patient allocation to groups and failure to randomize
Blinding of patients	Subjectivity in reporting symptoms Search for alternatives, that is, co-interventions
Blinding of health care providers	Offer of co-interventions
Blinding of outcome assessor	Subjectivity in outcome assessment, especially subjective
Missing/ Incomplete data	Difference in losses between groups and difference in reasons may mean that the losses were influenced by the alternatives evaluated (e.g. low efficacy or adverse treatment events)
Selective reporting of outcomes	Selection of favorable results
Outcome measurement	Selection of unreliable, reproducible or unusual method in clinical practice

Based and adapted from Spencer et al. (2020).

blinding of the outcome assessors, randomization method and allocation concealment weakens the confidence in the conclusions (Pacheco et al., 2020).

Then, Gautret et al. (2020) released an open, non-randomized clinical trial on March 20, 2020. Based on an analysis of 42 participants, considering as outcome the virological clearance, the authors found discordant results, suggesting superiority of HCQ in monotherapy or associated with azithromycin in relation to the standard treatment. The lack of randomization, blinding patients, health care providers and outcome assessors, missing data, and analysis per protocol are identified as being important methodological limitations that weaken confidence in the findings (Kim et al., 2020).

Lastly, on March 31, 2020, the randomized clinical trial with 62 participants conducted by Chen et al. (2020b) did not evaluate virological cure, but suggests radiological improvement (pneumonia) with HCQ. Although the study was randomized and did not present losses of patients, a high risk of bias was identified for selective reporting of outcomes, due to reporting outcomes not previously defined. In addition, there is uncertainty about the allocation concealment method, blinding patients, health care providers and outcome assessors (Pacheco et al., 2020).

It is also worth mentioning other aspects that reduce confidence in the evidence of clinical trials and go beyond the methodological quality, which are: i) the heterogeneity of the results due to differences in the population (e.g. severity of the disease, comorbidities, age, sex), and of the intervention and comparator (e.g. doses, duration, composition of standard treatment); ii) imprecision (i.e. reduced statistical power of analyzes with reduced sample sizes and wide confidence intervals); iii) publication bias, requiring more studies to assess whether there is selective publication of studies favorable to intervention; iv) indirect evidence, that is, whether the identified results are direct to the question (Guyatt et al., 2008). In this criterion, it is likely that there are the biggest limitations, because if the studies evaluate patients without comorbidities or in some cases with the mild form of the disease, how reliable is the relationship of these findings with the population most affected by COVID-19 (i.e. patients with comorbidities)? Furthermore, it is possible based on surrogate outcomes (e.g. virological cure) to infer that benefits for primary outcomes will be identified (e.g. clinical cure, mortality, time to disintubation, time in critical care unit, time in hospital)? (Table 3).

So, despite the race against time, it is necessary to wait results of larger and better designed studies. Until 10/04/2020,

Table 3. Potential impact of methodological limitations in clinical trials.

Presence of	High risk of
Methodological limitations	The findings are not consistent for the population included in the study
Heterogeneity or inconsistency	The findings are not extrapolable to a specific population or comparison
Publication bias	Studies with unfavorable results to the intervention are not published due to the motivations of researchers, financiers, journals
Indirect evidence	The findings do not specifically answer the questions of decision makers
Imprecision	Low statistical power and larger studies present divergent results

Based and adapted from Spencer et al. (2020); Guyatt et al. (2008).

there were 927 trials registered at the WHO-ICTRP, of which 79 on CQ or HCQ, not canceled (World Health Organization, 2020). In Brazil, until 4/4/2020, ethics committees approved 53 studies for COVID-19, of which six are on CQ or HCQ (Brasil, 2020d). From the perspective of health technology assessment (HTA), regulators, managers, prescribers, patients and so many other stakeholders are specialists and decision makers in health, as important as the development of adequate studies is transparent and accessible disclosure to society of these findings and their implications (Goodman, 2014).

Consequences and concerns

The consequences of the dissemination of the studies about HCG and CQ in COVID-19 treatment, for the scientific community and society have not gone unnoticed. After disclosing the study conducted by Gautret et al. (2020), the President Trump claimed that the combination of HCQ and azithromycin had a real chance of being one of the biggest changes in medical history. In Brazil, President Jair Bolsonaro opposed the recommendations of the WHO and the Brazilian Ministry of Health itself for social isolation, suggesting that CQ and HCQ would reduce the potential impacts of 'little flu'. The anxiety about being a spokesperson for the good news is understandable. However, the impact of this information should be considered. After the ads, there was an increase in searches for terms related to CQ, HCQ and scarcity (Kim et al., 2020); and reports of deaths and intoxications were also released (Agence Nationale de Sécurité du Médicament et des Produits de Santé, 2020).

The impact of irresponsible self-medication was as regrettable as it was predictable, after all, the decades of experience with these medicines for patients with malaria, rheumatoid arthritis, lupus erythematosus reveals that in lower doses than the proposals for treatment of COVID-19, however in treatment courses larger, CQ and HCQ can cause prolongation of the QTc interval (especially in patients with pre-existing heart disease or if associated with azithromycin), hypoglycemia, neuropsychiatric effects, drug interactions and idiosyncratic hypersensitivity reactions (Juurlink, 2020).

Other risks are the false sense of security, deprivation of patients to benefit in the future from promising alternatives such as plasma, immunosuppressants, antivirals, with an emphasis on antiretrovirals, immunobiologicals (Brasil, 2020a) and, not least, the shortage of drugs for approved indications.

In this sense, in Brazil, the National Health Surveillance Agency (Anvisa) authorized the use of CQ and HCQ at medical discretion and, therefore, capable of being used in clinical studies with Brazilians. At the same time, Anvisa increased the control of dispensation through the RDC 351/2020 (Brasil, 2020b), and RDC 354/2020 (Brasil, 2020c), which included CQ and HCQ in the C1 list of medicines and therefore, subject to special control recipe in two copies. By way of comparison, US Food Drug and Administration has authorized the emergency use of oral QC and HCQ formulations for the treatment of COVID-19 (U.S. Food and Drug Administration, 2020), while European Medicines Agency has authorized only for use in clinical trials or use programs emergency (European Medicines Agency, 2020).

Thus, what the evidence tells us is that it is not a matter of restricting access to a technology that is proven to be effective and safe, but rather controlling access to a technology under evaluation that can indeed prove benefits as long as well-designed studies are completed and disseminated. The assumptions of evidence-based health and HTA must be maintained even in times of international emergency with the risk that in the future we will have to deal with the complications of COVID-19, as well as the irrational use of these drugs.

RESUMO

Uso racional de cloroquina e hidroxicloroquina em tempos de COVID-19

Com a pandemia de COVID-19 instalada, parte dos esforços dos pesquisadores tem sido nos estudos de reposicionamento de cloroquina (CQ) e hidroxicloroquina (HCQ), medicamentos baratos e conhecidos há décadas para malária, artrite reumatoide e lúpus eritematoso sistêmico. Autoridades de saúde chinesas e sul-coreanas recomendaram o uso de CQ e HCQ para profilaxia e tratamento de COVID-19, incentivando pesquisadores do mundo a avaliar o potencial dos medicamentos como antivirais. Até o momento, foram divulgados resultados de três ensaios clínicos. Dois estudos apresentam resultados divergentes para depuração viral, enquanto o terceiro sugere benefício em termos de melhora radiológica e clínica. Os três estudos apresentam limitações metodológicas e baixa qualidade geral da evidência, tendo em vista ausência de randomização, sigilo de alocação, mascaramento de pacientes, profissionais de saúde ou avaliadores, perda de dados e/ou reporte seletivo de resultados, bem como provável heterogeneidade dos pacientes e tratamentos,

imprecisão devido ao reduzido poder estatístico dos estudos, evidência indireta para pacientes com forma grave da doença ou portadores de comorbidades de alta gravidade. A automedicação irresponsável destes medicamentos é motivo de preocupação tanto pelo potencial risco de desabastecimento, quanto pelos eventos adversos e intoxicações fatais potenciais. Dessa forma, nos EUA, Europa e Brasil, as agências reguladoras se posicionaram autorizando em caráter emergencial o uso de CQ e HCQ sob critério médico e/ou no contexto de ensaios clínicos. No Brasil, para coibir a automedicação irresponsável e possível desabastecimento, a Anvisa incluiu os medicamentos em lista de controle especial. A evidência sobre a eficácia e a segurança de CQ e HCQ permanecem incertas, de forma que os resultados dos estudos em andamento são necessários para orientar adequadamente as políticas públicas e prática clínica. Os pressupostos da saúde baseada em evidências devem ser mantidos mesmo em épocas de emergência internacional com o risco de no futuro termos que tratar as complicações do uso irracional destes medicamentos.
Palavras-chave: Política Informada por Evidências. Prática Clínica Baseada em Evidências. Vírus da SARS.

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