Received: 30 April 2020 | Revised: 19 August 2020 | Accepted: 26 August 2020

DOI: 10.1111/jep.13484

BRIEF REPORTS

Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

WILEY

Hydroxychloroquine for prophylaxis of COVID-19 physicians survey: Despite lack of evidence, many would take or give to dear ones, and despite the perceived necessity of an RCT, few would participate

Cristian Baicus MD, PhD[1,2,3] | Larisa Pinte MD[1,2,3] | Laura E. Stoichitoiu MD[1,3] | Camelia Badea MD, PhD[1,2]

[1]Department of Internal Medicine, Colentina Hospital, Bucharest, Romania

[2]University of Medicine and Pharmacy Carol Davila Bucharest, Bucharest, Romania

[3]Clinical Research Unit, Reseau d'Epidemiologie Clinique International Francophone, Bucharest, Romania

Correspondence
Laura E. Stoichitoiu, Department of Internal Medicine, Colentina Hospital, Soseaua Stefan cel Mare 19-21, sector 2, 020125 Bucharest, Romania.
Email: laura.elena.stoich@gmail.com

Abstract

Introduction: There was no evidence concerning the prophylaxis with hydroxychloroquine, and only low-grade evidence regarding the use of hydroxychloroquine as a treatment for COVID-19 patients. We performed a survey among Romanian physicians in order to see how many of them would administer prophylactically hydroxychloroquine to themselves or to people close to them, and if they would participate to a randomized controlled trial.

Methods: Between March 30 and April 02, 2020, a 16-item questionnaire was shared in a Romanian Facebook group of 2645 physicians dedicated to COVID-19 information, asking to be completed by physicians who could be directly involved in the care of these patients.

Results: A total of 785 answers were collected. Nine physicians (1.1%) thought that there was clear evidence on prescribing hydroxychloroquine prophylaxis, 375 (48%) considered the evidence acceptable, 348 (44.3%) considered it weak, whereas 53 (6.8%) answered there was no evidence. 59 (7.5%) respondents were determined to take it (of which 31 = 4% already took), 192 (24.5%) were inclined to take, 271 (34.5%) were not decided yet. 175 (22.3%) of respondents declared they (would) give the treatment to their close ones, and this decision was associated with a higher age (P = 0.003), and the opinion that there was evidence (P < 0.001). When asked about the source of the treatment regimen, 286 (36.4%) indicated a scientific paper, while no scientific paper about the prophylaxis with hydroxychloroquine existed at that time.

718 (91.5%) considered a randomized clinical trial necessary (RCT), but only 333 (42.4%) answered they would enrol in such a trial. There was only a very weak correlation (Kendall's tau _b = 0.255, P < 0.001) between the belief that an RCT is necessary and the willingness to enrol in such an RCT.

Conclusions: Despite the lack of evidence, many physicians considered the evidence as existing, and were ready to take or to give hydroxychloroquine prophylactically to family. They considered an RCT necessary, but they were not willing to participate.

KEYWORDS

COVID-19, hydroxychloroquine, physicians, prophylaxis, randomized controlled trial, survey

1 | INTRODUCTION

An outbreak of severe cases of pneumonia was recorded in Wuhan, China in December 2019.

It was not until February 26th that Romania reported the first case of SARS-CoV-2 infection.

After 1 month, on March 30th, we reached a total of 1952 cases and 44 deaths.

285 (14.6%) healthcare workers (HCWs) had already been tested positive for the novel coronavirus. Preclinical data suggested that hydroxychloroquine (HCQ) and chloroquine have in vitro antiviral activity against SARS-CoV-2.[1] On the 20th of March, the first small, observational study of Raoult's team[2] was published online, and as it is known, this study produced a lot of scientific and political turmoil. On the 21st of March, the Indian Council of Medical Research recommended the use of HCQ as prophylaxis for SARS-CoV-2 infection[3]; 76% of the Indian physicians followed the recommendation,[4] although many of them also criticized it as relying on weak evidence.[5] Until the moment we run our survey, no study had been conducted regarding the use of HCQ as prophylaxis.[6] A total of 22 studies including HCWs were registered on clinicaltrials.gov, and 6 of them were already recruiting subjects.[7]

On May 31st, Chatterjee et al published a case-control study, in which they found an association between HCQ administration and a lower risk of disease[8]; this study was the first one to suggest the prophylactic efficacy of HCQ among HCWs. On the other hand, continuous treatment with HCQ did not prevent SARS-CoV-2 infection in a large database analysis.[9] In the light of recent information on the topic,[10,11] on July 30th, the American College of Physicians retired their previous living practice points, which were recommending the use of HCQ for the prophylaxis or the treatment of coronavirus disease 2019.[12] The only randomized controlled trial (RCT) regarding this subject, which appears to be completed, is the one conducted by the University of Minnesota, but their results are yet unpublished.[13]

Concerning the safety of HCQ given as post-exposure or pre-exposure prophylaxis, an analysis of 2795 outpatients participating in three clinical trials showed frequent gastrointestinal side effects, but no more serious side effects than in the placebo group.[14]

The aim of the study was to assess if physicians took/would take themselves or prescribe to people close to them HCQ for the prophylaxis of infection/pulmonary complications with SARS-CoV-2 in the perspective of the existing evidence at that time. Also, we wanted to see if they considered an RCT necessary, and if they would agree to participate in such a trial.

2 | METHODS

From March 30 to April 02, 2020, we conducted an online survey on Facebook. The questionnaire was shared in a group created on the eighth of March in order to facilitate the exchange of information concerning COVID-19, which consisted of 2645 Romanian physicians. The questionnaire was composed by 14 items, and at the end of the questionnaire, there was an open question in which the participants were invited to explain why they would (not) enrol in an RCT. Comments were transcribed and coded according to the topic using thematic analysis.

Variables were presented as number (frequency) for the categorical variables, and median (minimum, maximum) for scale or ordinal variables without normal distribution. Because the distribution of the scale or ordinal variables was not normal, we used nonparametric tests: Mann-Whitney *U* for comparisons, and Kendall's tau_b for correlations. For the determinants of the decision to take or to give the drug to people close to the respondent physician, we used multivariable analysis (logistic regression); the independent variables introduced into the two models were age, gender, specialty, professional degree, the perceived strength of the evidence, and the source of the treatment regimen. We used the forward method because of the small number of people who took the drug.

Considering there were 2975 physicians in the group, for a confidence level of 95%, an error of +/−3% and a worst-case prevalence of 50%, we calculated a sample size of 748.

The identity of the respondents from social media is not revealed for questionnaires in Survey Monkey, and the completion of the questionnaire was decided by each participant; therefore, the Colentina Hospital Institutional Review Board considered the study to be exempt.

3 | RESULTS

There were 785 self-selected participants, 35% senior physicians, 31% specialists, and 34% residents, most of them women (611, 78%). Their specialities were 90 (11.5%) internal medicine, 85 (10.8%) surgical specialities, 64 (8.2%) cardiology, 57 (7.3%) rheumatology, 51 (6.5%) family medicine, 32 (4.1%) critical care, 28 (4.1%) infectious diseases, 328 (41.7%) other medical specialities, while the rest of 50 (6.4%) had other specialities like laboratory medicine, pathology, radiology, and so on. The age range was 25 to 69, mean = 38y, median 35. 45 (5.7%) were already treating COVID-19 patients, 277 (35.3%)

thought they would treat COVID-19 and 398 (50.7%) did not know whether they would treat or not.

Only 37 (4.7%) did not hear about HCQ prophylaxis of SARS-CoV-2 infection.

Based on their prior knowledge, 9 (1.1%) thought there was clear evidence on prescribing HCQ prophylaxis, 375 (48%) considered the evidence acceptable, 348 (44.3%) considered it weak, whereas only 53 (6.8%) answered that there was no evidence (the question referred only to the benefit of HCQ, and not to the evidence of harm, or the benefit/harm ratio). Women were more prone to consider there is evidence (P = <0.001). 59 (7.5%) respondents were determined to take HCQ (of which 31 = 4% already did), 192 (24.5%) were inclined to take it, 271 (34.5%) were not decided yet, while 261 (33.3%) were inclined or determined not to take it. The decision to take HCQ was associated with a higher age (P = 0.02), the belief that an RCT would be necessary (P < 0.001), but not with the willingness to enrol in such an RCT (P < 0.858).

175 (22.3%) of respondents declared that they (would) give the treatment to their close ones, and this decision was associated with a higher age (P = 0.003), the opinion that there is evidence (Kendall's tau_b = 0.269, P < 0.001), the belief that an RCT would be necessary (P = 0.01), but not with the willingness to enrol in such an RCT (P = 0.420).

In multivariable analysis, the decision to take the drug remained associated only with age and the source of the regimen, while the decision to treat family/friends was also associated with the perceived strength of evidence (Table 1).

The therapeutic regimen differed from 800 mg/day, to 200 mg every 3 weeks, but the most indicated was 800 mg the first day, followed by 400 mg weekly. When asked about the source of the treatment regimen, 286 (36.4%) stipulated a scientific paper, 54 (7%) indicated a colleague, 27 (3.4%) had their own conceived regimen, while 87 (11%) found it on the internet.

718 (91.5%) deemed an eventual RCT necessary. However, when asked if they would enrol in such a trial, only 333 (42.4%) answered they would. There was only a very weak correlation (Kendall's tau _b = 0.255, P < 0.001) between the belief that an RCT is necessary and the willingness to enrol in such an RCT.

Of 785 respondents, 532 (67.8%) answered the open-ended question. We identified two major themes regarding the relation between physicians' need to promote medical research and their willingness to enrol actively in a trial considered useful: the balance between the "greater good" and personal risks, and the unavoidable harshness of dealing with the unknown. Their unwillingness to enrol in an RCT was justified by two different types of fears. For physicians who would take prophylaxis, the main driver was the fear of no treatment ("I would prefer to take prophylaxis if I would treat COVID patients; I can't afford the risk of taking placebo"). For people who would not take HCQ, the decisive factor was the fear of adverse reactions ("I think that for me, the adverse reactions of HCQ would be more serious than COVID-19"); besides, some considered that self-good is more important, advocating reasons like "out of commodity" and "I am not a lab rat". Physicians willing to enrol considered that evidence-based medicine and saving lives come first, stating "I am a physician. I am ready to contribute with whatever is needed in order to combat or to develop the prophylaxis against SARS-CoV-2". Physicians were torn apart between denial and hope, between their unwillingness to admit that HCQ has no proven positive effects and their forged hope, stating "I prefer to think that it has an effect, even a minimum one, than believing there is no treatment"; consequently, they decided not to enrol. Moreover, the perceived futility of breaking the unknown influenced their decision in a negative fashion, considering that if common sense indicates that a drug should not have a certain effect, it should not further be investigated "For the moment, because I do not understand the concept of prophylaxis with a drug which does not have an effect proven to be strictly antiviral".

4 | DISCUSSION

Half of the participants considered that the evidence was clear or acceptable, but only a third of the physicians were decided or inclined

TABLE 1 Logistic regression—determinants for taking hydroxychloroquine her(him)self, and administering hydroxychloroquine to someone close, adjusted for age, gender, professional degree, specialty, perceived strength of evidence and source of the treatment regimen

	Taking hydroxychloroquine her(him)self			Administering hydroxychloroquine to someone close		
Variable	**B**	***P***	**OR (95% CI)**	**B**	***P***	**OR (95% CI)**
Age	0.052	**0.003**	1.05 (1.02-1.1)	0.019	**0.040**	1.02 (1.0-1.04)
The source of the regimen		**0.021**			**0.001**	
Scientific paper/own regimen	2.040	**0.049**	7.7 (1.00-59)		0.346	
Scientific paper/other	2.7968	**0.007**	16.4 (2.17-125)	0.894	**<0.001**	2.4 (1.5-3.9)
Scientific paper/colleague		0.804			0.161	
Scientific paper/internet		0.935			0.359	
How strong is the evidence?		0.801			**<0.001**	
Weak evidence/no evidence					0.149	
Acceptable evidence/no evidence				2.031	**0.001**	7.6 (2.3-25.4)
Strong evidence/no evidence				2.273	**0.015**	9.7 (1.6-60.3)

Note: Statistically significant results are bold.

to take HCQ prophylactically, and a quarter were decided to administer it to family members/friends. The main drivers for the decision of not taking HCQ, in spite of considering that the evidence supported its prophylactic use, were the fear of adverse reactions, and the fact that they had comorbidities, which made them more prone to developing HCQ toxicity. Pregnancy and breastfeeding were also a reason for refusing prophylactic treatment. Most of the participants who would take or prescribe HCQ, believed that there was some kind of evidence concerning the prophylaxis with HCQ, when in fact, at the time, there was not. Apparently, this opinion was one of the drivers to taking/administering HCQ prophylactically. The lack of evidence is also reflected by the diversity of treatment regimens, and the declared source of the regimen (own regimen, from a colleague, found on the internet); 36% of physicians declared that they had taken the regimen from a scientific article, but there was no such scientific article at that time. This attitude could have originated from the lack of critical appraisal skills[15] or from the fact that being in the frontline of a pandemic could have made physicians more inclined to believe less reliable sources and, as consequence, give them value of evidence-based medicine.[16] On the other hand, physicians recommend different treatments for themselves than they would choose for patients, possibly not considering evidence when dealing with themselves or their dear ones.[17,18]

Regarding the utility of an RCT for the assessment of HCQ given prophylactically, almost all of them considered such a trial necessary, but less than a half of them would have enrolled.

The main limitation of the study consists in the fact that the survey was performed on Facebook, on self-selected participants; therefore, it is hard to appreciate the representativeness of the sample.

ACKNOWLEDGEMENTS

There was no funding for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Laura E. Stoichitoiu https://orcid.org/0000-0002-0234-0856

REFERENCES

1. Grau-Pujol B, Camprubí D, Marti-Soler H, Fernández-Pardos M, Guinovart C, Muñoz J. Pre-exposure prophylaxis with hydroxychloroquine for high-risk healthcare workers during the COVID-19 pandemic: a structured summary of a study protocol for a multicentre, double-blind randomized controlled trial. *Trials*. 2020;21(1):688. https://doi.org/10.1186/s13063-020-04621-7.
2. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;56(1):105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.
3. https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf. Accessed April 15, 2020.
4. Gangopadhyay KK, Sinha B, Ghosal S. Compliance of the Indian National Task Force guidelines for COVID-19 recommendation by Indian doctors—a survey [published online ahead of print, July 25, 2020]. *Diabetes Metab Syndr* 2020;14(5):1413–1418. https://doi.org/10.1016/j.dsx.2020.07.040
5. Bmj India Correspondent. Covid-19: Doctors criticise Indian research agency for recommending hydroxychloroquine prophylaxis. *BMJ*. 2020;369:m2170. https://doi.org/10.1136/bmj.m2170.
6. Shah S, Das S, Jain A, Misra DP, Negi VS. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in Coronavirus Disease-19 (COVID-19) [published online April 13, 2020]. *Int J Rheum Dis* 2020;23(5):613-619. https://doi.org/10.1111/1756-185X.13842
7. *ClinicalTrials.gov. Search of: plaquenil | COVID | Studies that accept healthy volunteers - List Results*. https://clinicaltrials.gov/ct2/results?term=plaquenil&cond=COVID&age_v=&gndr=&hlth=Y&type=&rslt=&Search=Apply. Accessed April 15, 2020.
8. Chatterjee P, Anand T, Singh KJ, et al. Healthcare workers & SARS-CoV-2 infection in India: a case-control investigation in the time of COVID-19. *Indian J Med Res*. 2020;151(5):459-467. https://doi.org/10.4103/ijmr.IJMR_2234_20.
9. Gendelman O, Amital H, Bragazzi NL, Watad A, Chodick G. Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: insights from a large healthcare database analysis. *Autoimmun Rev*. 2020;19(7):102566. https://doi.org/10.1016/j.autrev.2020.102566.
10. Rakedzon S, Khoury Y, Rozenberg G, Neuberger A. Hydroxychloroquine and coronavirus disease 2019: a systematic review of a scientific failure. *Rambam Maimonides Med J*. 2020;11(3):e0025. https://doi.org/10.5041/RMMJ.10416
11. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ*. 2020;370:m2980. Published 2020 Jul 30. https://doi.org/10.1136/bmj.m2980
12. Qaseem A, Yost J, Etxeandia-Ikobaltzeta I, Humphrey LL. Update alert 2: should clinicians use chloroquine or hydroxychloroquine alone or in combination with azithromycin for the prophylaxis or treatment of COVID-19? Living Practice Points From the American College of Physicians [published online ahead of print, 2020 Jul 30]. *Ann Intern Med* 2020;173(5):W88- W89. https://doi.org/10.7326/L20-1007
13. https://clinicaltrials.gov/ct2/show/NCT04328467. Accesed August 14, 2020.
14. Lofgren SMM, Nicol MR, Bangdiwala AS, et al. Safety of hydroxychloroquine among outpatient clinical trial participants for COVID-19. Preprint. *medRxiv*. July 16, 2020.20155531. Published 2020 Jul 23. https://doi.org/10.1101/2020.07.16.20155531
15. Swennen MHJ, van der Heijden GJMG, Boeije HR, et al. Doctors' perceptions and use of evidence-based medicine: a systematic review and thematic synthesis of qualitative studies. *Acad Med*. 2013;88:1384-1396. https://doi.org/10.1097/ACM.0b013e31829ed3cc.
16. Naylor CD. Grey zones of clinical practice: some limits to evidence-based medicine. *Lancet*. 1995;345(8953):840-842. https://doi.org/10.1016/s0140-6736(95)92969-x.
17. Ubel P, Angott AM, Zikmund-Fisher BJ. Physicians recommend different treatments for patients than they would choose for themselves. *Arch Intern Med*. 2011;171:630-634. https://doi.org/10.1001/archinternmed.2011.91.
18. Baicus C, Delcea C, Dima A, Oprisan E, Jurcut C, Dan GA. Influence of decision aids on oral anticoagulant prescribing among physicians: a randomised trial. *Eur J Clin Invest*. 2017;47:649-658. https://doi.org/10.1111/eci.12786.

How to cite this article: Baicus C, Pinte L, Stoichitoiu LE, Badea C. Hydroxychloroquine for prophylaxis of COVID-19 physicians survey: Despite lack of evidence, many would take or give to dear ones, and despite the perceived necessity of an RCT, few would participate. *J Eval Clin Pract*. 2020;26:1579–1582. https://doi.org/10.1111/jep.13484