Hydroxychloroquine and Chloroquine in COVID-19

A Survey of Prescription Patterns Among Rheumatologists

Bella Mehta, MBBS, MS,† Carine J. Moezinia, MBBS,* Deanna Jannat-Khah, DrPH,*† Allan Gibofsky, MD,* Haley Tornberg, BS,* Diyu Pearce-Fisher, BS,* Susan M. Goodman, MD,*† Jane E. Salmon, MD,* and Said Ibrahim, MD†‡*

Objective: With hydroxychloroquine (HCQ) and chloroquine (CQ) emerging as potential therapies for coronavirus disease 2019 (COVID-19), shortages have been reported. We aimed to understand how rheumatologists, one of the most common prescribers of HCQ/CQ, prescribed these medications to manage COVID-19 and to understand if their patients are affected by shortages.

Methods: Between April 8 and April 27, 2020, an online survey was distributed to a convenience sample of rheumatologists who practice medicine in a diverse range of settings globally, resulting in 506 responses. Adjusted Poisson regression models were calculated.

Results: Only 6% of respondents prescribed HCQ/CQ for COVID-19 prophylaxis, and only 12% for outpatient treatment of COVID-19. Compared to the United States, the likelihood of prescribing HCQ/CQ for prophylaxis was higher in India (adjusted risk ratio [aRR], 6.7; 95% confidence interval [CI], 2.7–16.8; $p < 0.001$). Further, compared to the United States and those with 1 to 5 years of experience, rheumatologists in Europe (aRR, 2.9; 95% CI, 1.6–5.3; $p < 0.001$) and those with 10+ years of experience (11–20 years: aRR, 2.5; 95% CI, 1.2–5.3; $p = 0.015$; 21+ years: aRR = 3.3; 95% CI, 1.4–7.4; $p = 0.004$) had a higher likelihood of prescribing HCQ/CQ for outpatient treatment. Of note, 71% of all rheumatologists reported that their patients were directly affected by HCQ/CQ shortages.

Conclusion: The results suggest that only a small percentage of rheumatologists are prescribing HCQ/CQ for prophylaxis or outpatient treatment of COVID-19. Medication shortages experienced by large numbers of autoimmune disease patients are concerning and should play a role in decisions, especially given poor efficacy data for HCQ/CQ in COVID-19.

Key Words: chloroquine, COVID-19, hydroxychloroquine, rheumatologist, survey

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The coronavirus disease 2019 (COVID-19) pandemic caused by the novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS–CoV-2]/2019-nCoV) has created a severe global public health crisis and economic disruption. Hydroxychloroquine (HCQ) and chloroquine (CQ) have emerged as potential therapies repurposed for COVID-19.[1,2] However, to date, there has been a lack of conclusive efficacy data in vivo,[3,4] and there are now early reports of potential toxicity and harm.[5,6] While randomized clinical trial results were pending, the US Food and Drug Administration on March 28, 2020, issued an Emergency Use Authorization of CQ and HCQ for the treatment of hospitalized COVID-19 patients.[7] This Emergency Use Authorization had global implications. Currently, most countries do not recommend HCQ and CQ for prevention and outpatient treatment of COVID-19, with the exception of a few countries, such as India.[8]

Hydroxychloroquine and CQ are inexpensive drugs that have been in use for decades. While CQ is additionally used for malaria prophylaxis and treatment, its less toxic metabolite, HCQ, is prescribed primarily for autoimmune diseases. As a result, CQ is predominantly prescribed by primary care physicians and infectious disease specialists, while both HCQ and CQ are routinely prescribed by rheumatologists for chronic autoimmune diseases.[9] Following media coverage and the touting of HCQ/CQ efficacy by various influential figures,[10] there have been reports of a surge in HCQ/CQ prescriptions,[9] resulting in shortages for autoimmune disease patients who regularly take these medications.[11]

Given both the questionable nature of the clinical evidence surrounding the off-label use of HCQ and CQ for COVID-19 and supply shortages affecting autoimmune patients, rheumatologists now find themselves in a challenging position during this pandemic.[12] Our objective was to understand how rheumatologists worldwide are prescribing HCQ/CQ for the prevention and outpatient treatment of COVID-19 and whether their patients are experiencing medication shortages.

MATERIALS AND METHODS

We conducted an online survey of a convenience sample of rheumatologists who practice medicine in diverse settings worldwide. This survey was administered from April 8 to April 27, 2020, while media attention on HCQ/CQ continued.[10] The survey was built on an online platform (surveygizmo.com) and broadcasted over social media platforms, including LinkedIn, Twitter, Facebook, ResearchGate, and WhatsApp. It was distributed by email to rheumatology-specific groups and societies for broad outreach. The survey relied on voluntary self-reporting when the survey was seen on social media posts or group emails and required that respondents must be rheumatologists (trainees included). We included responses from both adult and pediatric rheumatologists.

The questionnaire, written in English, consisted of demographics and 3 HCQ/CQ-related questions. Other questions, which are not reported here, will be discussed separately. Demographic variables of interest included participant gender, country of practice, years in rheumatology practice, and practice setting.

Descriptive statistics such as frequencies and percentages are presented. Bivariate comparisons were performed using Fisher

From the *Hospital for Special Surgery; †Weill Cornell Medicine; and ‡Weill Cornell Health Policy and Research, New York, NY.

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Ethics committee approval was granted from HSS institutional review board (#2020-0520). Data are available upon reasonable request from corresponding author, B.M. Reuse is permitted upon proper referencing of the source of the data using the unique identifier. Data are in a deidentified participant state.

Correspondence: Bella Mehta, MBBS, MS, Hospital for Special Surgery, 535 E 70th St, New York, NY 10021. E-mail: drbellamehta@gmail.com.

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exact test. Poisson regression models, using robust standard errors, were calculated and adjusted for physician gender, years of rheumatology practice, country, and type of rheumatology practice. Statistical significance was determined using an α of 0.05, and all analyses were conducted using Stata version 14 (StataCorp LP, College Station, TX)

The institutional review board of the Hospital for Special Surgery (HSS) approved the anonymized survey and protocol.

RESULTS

The Table summarizes the characteristics of the sample. A total of 506 rheumatologists from 61 countries responded to the HCQ/CQ survey, with 49% (n = 247) from the United States, 31% (n = 157) from Europe, 7% (n = 33) from India, and 13% (n = 68) were from the remaining countries grouped as "other." The respondents were from a wide distribution of practice experience (posttraining 1–5 years: 30%; 6–10 years: 20%; 11–20 years: 18%; 21+ years:17%; and 15% were in training). A majority (71%) of respondents were in academic or governmental-based practices, whereas the remaining were from a range of private practice settings (Table).

When asked, "Have you prescribed hydroxychloroquine or chloroquine to prevent COVID-19 for a nonhospitalized patient who was not previously on it?" 94% responded "no." Of the 6% who responded "yes," 33.3% were in the United States, 23.3% were in Europe, 36.7% were in India, and 6.7% were in other countries. Compared to the United States, the likelihood of prescribing HCQ/CQ for COVID-19 prophylaxis was higher in India (aRR, 6.7; 95% confidence interval [CI], 2.7–16.8; $p < 0.001$). There was no statistically significant difference between years posttraining and HCQ/CQ prophylaxis prescription patterns (Figs. 1A, B).

When asked, "Have you prescribed hydroxychloroquine or chloroquine to treat COVID-19, in a nonhospitalized patient who was not previously on it?" again approximately 88% responded "no." Of the 12% who responded "yes," 36.7% were in the United States, 43.3% were in Europe, 10% were in India, and 10% were in other countries. Compared to the United States, the likelihood of prescribing CQ/ HCQ for COVID-19 treatment was higher in Europe (aRR, 2.9; 95% CI, 1.6–5.3; $p < 0.001$). Furthermore, compared to those who are 1 to 5 years post–clinical training, those 11 to 20 years (aRR, 2.5; 95% CI, 1.2–5.3; $p = 0.015$) and 21 years or more (aRR, 3.3; 95% CI, 1.4–7.4; $p = 0.004$) post–clinical training had a higher likelihood of prescribing HCQ/CQ for COVID-19 treatment (Figs. 2A, B).

To assess how HCQ/CQ shortages have affected patients cared for by rheumatologists, we asked the question, "How many of your patients have been unable to obtain their regular hydroxychloroquine or chloroquine due to shortages?" 71% responded that at least some portion of their patients have been unable to obtain HCQ/CQ. Of these, approximately 54% had more than 5 patients who were unable to fill their regular prescription, and 13% reported that more than 30 of their patients were affected by this crisis. On the other hand, only 18% of the rheumatologists responded that there were no shortages (majority from India), and 11% responded "do not know".

DISCUSSION

In this survey of rheumatologists across the globe, performed during a time of unprecedented public interest in HCQ/CQ for the treatment and prophylaxis of COVID-19, we found that a majority of rheumatologists were not prescribing HCQ/CQ for prophylaxis or outpatient treatment. Additionally, a majority reported that drug

TABLE. Survey Respondent Characteristics

		Prescription of HCQ as Prophylaxis			Prescription of HCQ as Treatment		
	Total, n (%)	No	Yes	*p* value	No	Yes	*p* value
Sex				**0.01**			0.49
Female	261 (51.6)	253 (53.2)	8 (26.7)		234 (52.5)	27 (45.0)	
Male	213 (42.1)	192 (40.3)	21 (70.0)		183 (41.0)	30 (50.0)	
Do not want to specify	3 (0.6)	3 (0.6)	0 (0.0)		3 (0.7)	0 (0.0)	
Missing	29 (5.7)	28 (5.9)	1 (3.3)		26 (5.8)	3 (5.0)	
Country				**<0.001**			0.064
United States	247 (48.8)	237 (49.8)	10 (33.3)		225 (50.4)	22 (36.7)	
Europe	157 (31.0)	150 (31.5)	7 (23.3)		131 (29.4)	26 (43.3)	
India	33 (6.5)	22 (4.6)	11 (36.7)		27 (6.1)	6 (10.0)	
Other	68 (13.4)	66 (13.9)	2 (6.7)		62 (13.9)	6 (10.0)	
Missing	1 (0.2)	1 (0.2)	0 (0.0)		1 (0.2)	0 (0.0)	
No. years in practice				0.32			0.15
Currently in training	74 (14.6)	71 (14.9)	3 (10.0)		68 (15.2)	6 (10.0)	
1–5	151 (29.8)	145 (30.5)	6 (20.0)		140 (31.4)	11 (18.3)	
6–10	99 (19.6)	92 (19.3)	7 (23.3)		87 (19.5)	12 (20.0)	
11–20	93 (18.4)	88 (18.5)	5 (16.7)		78 (17.5)	15 (25.0)	
≥21	86 (17.0)	77 (16.2)	9 (30.0)		73 (16.4)	13 (21.7)	
Missing	3 (0.6)	3 (0.6)	0 (0.0)		0 (0.0)	3 (5.0)	
Practice type				**0.033**			1.00
Academic/government	359 (70.9)	343 (72.1)	16 (53.3)		316 (70.9)	43 (71.7)	
Private practice solo/group/hospital	139 (27.5)	125 (26.3)	14 (46.7)		123 (27.6)	16 (26.7)	
Missing	8 (1.6)	8 (1.7)	0 (0.0)		7 (1.6)	1 (1.7)	

*p values in bold font indicate significance, $p < 0.05$.

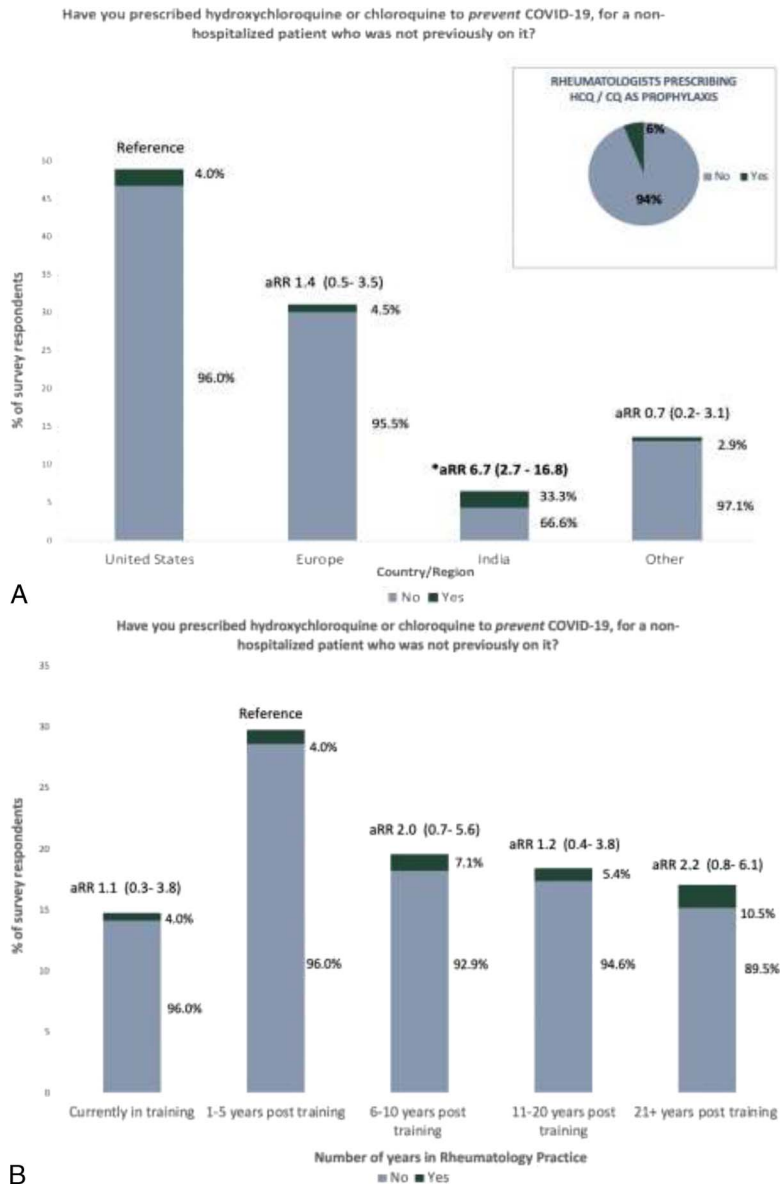

FIGURE 1. A and B, Responses from rheumatologists for prophylaxis of HCQ and CQ in COVID-19. A, Distribution by country. B, Distribution by number of years after training. Color online-figure is available at http://www.jclinrheum.com.

shortages have indeed affected their patients. We also found that there is a higher likelihood of the prescription of prophylactic HCQ/CQ in India, perhaps related to the fact that this country is home to several manufacturers of HCQ/CQ and its guidelines recommending prophylactic use for COVID-19. Finally, we found that as compared to US rheumatologists, as well as those with 1–5 years of experience, rheumatologists in Europe and those who are more than 10 years out of clinical training, respectively, have a higher likelihood of prescribing HCQ/CQ for outpatient treatment of COVID-19.

Our findings underscore reports that, prior to the pandemic, most HCQ/CQ prescriptions came from rheumatologists, dermatologists, and cardiologists. However, after these medications garnered widespread media attention, physicians from many disciplines began prescribing in record volumes.[9] Additionally, there were reports of drug hoarding, which exacerbated shortages in many areas.[13] Although there was an exponential rise in first-time prescribers of HCQ/CQ, prescriptions from rheumatologists remained relatively stable.[9] This may be explained by the deeper understanding rheumatologists have regarding the implications these drugs have for disease control and health-related quality-of-life improvement for patients with autoimmune diseases, such as those with lupus. A point to note is that after the survey had concluded, a study was published showing HCQ/CQ had no benefits against COVID-19 and even had potential cardiac toxicity, thereby increasing mortality. Although the article was subsequently retracted, it emphasizes the issue of how some studies and the media can mislead and influence the public perception of medications being trialed during this time, thereby leading to stockpiling or alarm.[14]

We found that European rheumatologists have a higher likelihood of prescribing HCQ/CQ for outpatient COVID-19 treatment compared to US rheumatologists. Some countries, namely, England, who contributed a large number of survey responses, were hit the hardest by COVID-19. Although their guidelines do

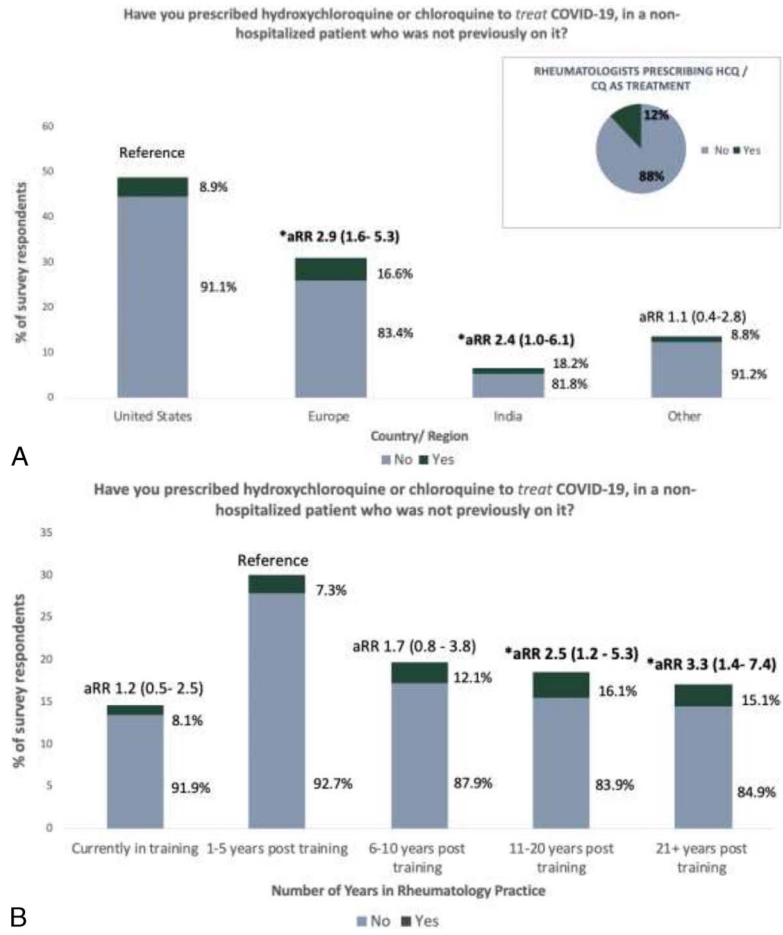

FIGURE 2. A and B, Responses from rheumatologists for treatment of HCQ and CQ in COVID-19. A, Distribution by country. B, Distribution by number of years after training. Color online-figure is available at http://www.jclinrheum.com.

not recommend HCQ/CQ, it is conceivable that the high mortality and morbidity rates experienced by these countries when the survey was conducted may have influenced the decision by rheumatologists to utilize these drugs.[15] We also discovered that experienced rheumatologists are more likely to prescribe HCQ/CQ for treatment compared to those with 1 to 5 years of experience. Perhaps less experienced rheumatologists are more prone to following guidelines, and/or experienced rheumatologists are comfortable prescribing short courses of HCQ/CQ.[16]

It is reassuring that rheumatologists, who are the most common prescribers of these drugs, did not demonstrate increased prescription patterns for COVID-19.[9] We hypothesize many reasons for this, including inconclusive data on the efficacy of HCQ/CQ in COVID-19, early reports of potential worse outcomes and toxicity,[5,6] and concern among rheumatologists that their patients are directly affected by drug shortages, potentially exposing them to great risks.[11]

There are important limitations to consider when interpreting our findings. First, it is difficult to obtain a robust survey response rate. This was an online survey that was advertised utilizing social media platforms and email campaigns, so we cannot estimate how many rheumatologists had the opportunity to participate. Of those whom the survey reached, the rheumatologists who chose to respond may reflect a respondent bias. There is also the inherent issue of response rate differences between United States–based rheumatologists and rheumatologists from other countries. This might be due partly to internet access or cultural variations in survey-based studies. Also, as this is a convenience sample, it may be difficult to generalize results. Lastly, it is important to note that it is possible COVID-19 prophylaxis and treatments are predominantly prescribed by infectious disease/primary care colleagues and less so by rheumatologists. However, it is likely that rheumatologists are involved in the decision to prescribe HCQ/CQ for patients with autoimmune diseases. Several strengths of this study include the large number of respondents and the diversity of countries, experiences, and practice settings represented.

Therefore, among rheumatologists, the major prescribers of HCQ/CQ, we do not see increased rates of prescriptions for prophylaxis and outpatient COVID-19 treatment. Additionally, the majority have at least some patients who are directly affected by medication shortages. As we wait for more conclusive data on the efficacy of HCQ/CQ in COVID-19, it is important to remind physicians to consider the effect of supply shortages on autoimmune patients who rely on these medications to prevent disease progression and serious end-organ damage.

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