# Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19

The use of hydroxychloroquine (HCQ) in the prophylaxis and treatment of coronavirus disease 2019 (COVID-19) has received significant attention by politicians and media figures. This has occurred despite limited data supporting its efficacy in COVID-19 as well as considerable concern about its safety when used at high doses (>400 mg daily) and in combination with other QT interval prolonging drugs.[1–4]

An inaccurate narrative has emerged in recent weeks that patients with systemic lupus erythematosus (SLE) who are taking HCQ as a baseline therapy are less affected by or do not develop COVID-19.[5–7] This assumption has been challenged by Monti and Montecucco,[8] referencing data from the COVID-19 Global Rheumatology Alliance registry on patients with rheumatic disease that previously identified 19/110 (17%) patients with SLE.[9] A case series of 17 patients with lupus or antiphospholipid syndrome who developed COVID-19 on a median HCQ dose of 400 mg daily (median HCQ blood level of 648 ng/mL) has since become available.[10] As of 17 April 2020, we have now identified 80 patients with SLE and COVID-19 in the global physician-reported registry. Patients were predominantly female (72/80, 90%) and less than 65 years of age (69/80, 86%). Importantly, 64% (51/80) of patients with SLE were taking an antimalarial (HCQ or chloroquine) prior to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (30% as monotherapy). Notably, 21.1% (121/573) of all reported patients with rheumatic disease in the registry were treated with an antimalarial prior to onset of COVID-19, yet 49.6% (60/121) required hospitalisation. In patients with SLE, frequency of hospitalisation with COVID-19 did not differ between individuals using an antimalarial versus non-users (55% (16/29) vs 57% (29/51), p=ns; $\chi^2$ test). In patients with lupus, escalation to maximum level of care (non-invasive ventilation, invasive ventilation or extracorporeal membrane oxygenation (ECMO)) was required regardless of HCQ use (online supplementary table S1). Thus, patients with lupus—even if they are using an antimalarial such as HCQ as baseline therapy—can develop SARS-CoV-2 infection and severe COVID-19 at similar frequency as lupus patients not on antimalarials.

There are currently >40 ongoing clinical trials examining HCQ in the prophylaxis or treatment of SARS-CoV-2 infection that employ highly variable strategies with regards to dosing (total oral loading dose 400–1400 mg), duration and time of initiation.[11] However, dosing considerations of HCQ in COVID-19 may be critical to understand why patients with lupus may not be protected from SARS-CoV-2 infection.

Similar to in vitro studies indicating activity of antimalarial 4-aminoquinoline derivatives against SARS-CoV-1 and MERS-CoV,[12 13] a putative role for HCQ in the treatment of COVID-19 has been suggested by its antiviral effect in cell culture systems.[14 15] Given the assumptions made when moving from a cell-based model to a complex in vivo system, in vitro potency cannot be expected to translate into in vivo efficacy,[16] as observed for chloroquine in a mouse model of SARS-CoV-1 infection.[17] To date, no in vivo exposure response data are available for HCQ in COVID-19. Few data are available to extrapolate what drug concentrations must be achieved to observe in vivo efficacy and in which compartment (eg, whole blood vs epithelial lining fluid vs lung parenchyma). Even for influenza and approved antiviral drugs (oseltamivir), the direct relationship between drug concentration and in vivo activity is uncertain.[18 19] Current in vitro data suggest that the concentration of HCQ at which 50% of the maximal activity against SARS-CoV-2 is obtained (EC50) is 0.72–4.51 µM (ie, ~242–1515 ng/mL),[14 15] similar to the EC50 observed in SARS-CoV-1 and MERS-CoV.[13] Ninety per cent inhibition of SARS-CoV-2 (EC90) with HCQ was achieved at ~5–15 µM (~1679–5038 ng/mL), while clearance required ~20 µM (~6717 ng/mL).[14 15] Importantly, both EC50 and EC90 concentrations may be insufficient to improve clinical outcomes. Instead, the concentration of HCQ required to *eliminate* SARS-CoV-2 may be a more meaningful target.[20] Such concentrations of HCQ (ie, ~6700 ng/mL), however, are not safely achievable in whole blood, and little is known about the concomitant concentrations obtainable in lung parenchymal cells in humans (assuming this represents a critical site for antiviral activity in COVID-19). Without an understanding of effective HCQ concentrations in target tissues, effective therapeutic doses remain difficult to predict by simulation. For dosing strategies to be informed, an intricate understanding of HCQ transfer constants between the blood and the lung tissue is required.

HCQ used in the treatment of SLE is typically prescribed at doses of 5.0–6.5 mg/kg, with a maximum dose of 400 mg daily. The majority of patients with SLE on chronic HCQ treatment do not achieve whole blood concentrations of 5–15 µM (~1679–5038 ng/mL),[10 21] corresponding to the EC90 for SARS-CoV-2.[14 15] While pulmonary drug concentrations in mice are known to reach much higher levels than in blood, these HCQ concentrations may be required to achieve meaningful antiviral activity in blood. The difficulty of achieving potentially meaningful blood concentrations at HCQ doses typically prescribed in SLE may have important implications for trial design in COVID-19 and needs to be considered when interpreting outcomes of these studies. Notably, results from an open-label, randomised, controlled trial using doses as high as HCQ 1200 mg for 3 days (followed by a maintenance dose of 800 mg daily for 2–3 weeks) did not suggest efficacy of HCQ in suppressing viral replication.[22] These efficacy data, and the irrefutable clinical data collected through the COVID-19 Global Rheumatology Alliance registry, establish that patients with lupus on baseline therapy with HCQ are not universally protected from COVID-19.

**Maximilian F Konig ,[1] Alfred HJ Kim ,[2,3,4] Marc H Scheetz,[5,6] Elizabeth R Graef,[7] Jean W Liew,[8] Julia Simard,[9] Pedro M Machado ,[10,11,12] Milena Gianfrancesco,[13] Jinoos Yazdany,[13] Daman Langguth,[14] Philip C Robinson ,[15] On behalf of the COVID-19 Global Rheumatology Alliance**

[1]Division of Rheumatology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[2]Division of Rheumatology, Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri, USA
[3]Division of Immunobiology, Department of Pathology and Immunology, Washington University School of Medicine, Saint Louis, Missouri, USA
[4]Andrew M. and Jane M. Bursky Center of Human Immunology and Immunotherapy Programs, Washington University School of Medicine, Saint Louis, Missouri, USA
[5]Departments of Pharmacy Practice and Pharmacology; Pharmacometrics Center of Excellence, Midwestern University, Chicago College of Pharmacy, and College of Graduate Studies, Downers Grove, Illinois, USA
[6]Department of Pharmacy, Northwestern Memorial Hospital, Chicago, Illinois, USA
[7]Division of Rheumatology and Clinical Immunology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
[8]Division of Rheumatology, Department of Medicine, University of Washington, Seattle, Washington, USA
[9]Department of Epidemiology & Population Health; Department of Medicine, Division of Immunology & Rheumatology, Stanford University School of Medicine, Stanford, California, USA

[10]Centre for Rheumatology & Department of Neuromuscular Diseases, University College London, London, UK
[11]Department of Rheumatology & Queen Square Centre for Neuromuscular Diseases, University College London Hospitals NHS Foundation Trust, London, UK
[12]Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK
[13]Division of Rheumatology, Department of Medicine, University of California San Francisco, San Francisco, California, USA
[14]Department of Immunology, Sullivan Nicolaides Pathology, Brisbane, Queensland, Australia
[15]The University of Queensland Faculty of Medicine, Brisbane, Queensland, Australia

**Correspondence to** Dr Maximilian F Konig, Division of Rheumatology, The Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA; konig@jhmi.edu and Dr Philip C Robinson, The University of Queensland Faculty of Medicine, Brisbane, Queensland, Australia; philip.robinson@uq.edu.au

**Handling editor** Josef S Smolen

**Twitter** Maximilian F Konig @MaxKonigMD, Alfred HJ Kim @alhkim, Marc H Scheetz @IDPharmacometrx, Pedro M Machado @pedrommcmachado and Philip C Robinson @philipcrobinson

**Collaborators** COVID-19 Global Rheumatology Alliance (full list of collaborators at: https://rheum-covid.org/about/)

**Contributors** MFK, DL and PCR conceptualised the article and drafted the manuscript. MG did the data analyses. All authors contributed to data interpretation, writing and final approval of the manuscript.

**Funding** MFK was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH) under Award no. T32AR048522 and received personal fees from Bristol-Myers Squibb and Celltrion, unrelated to this manuscript. AHK was supported by grants from NIH/NIAMS and Rheumatology Research Foundation and personal fees from Exagen Diagnostics, Inc and GlaxoSmithKline, unrelated to this manuscript. PMM is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre and received consulting or speaker's fees from Abbvie, Eli Lilly, Novartis and UCB Pharma. JY received personal fees from Astra Zeneca and Eli Lilly, unrelated to this manuscript. PCR reports personal fees from Abbvie, Pfizer, UCB Pharma, Novartis, Eli Lilly and Janssen and non-financial support from Roche.

**Disclaimer** The views expressed here are those of the authors and participating members of the COVID-19 Global Rheumatology Alliance, and do not necessarily represent the views of the American College of Rheumatology, the European League Against Rheumatism, or any other organisation.

**Competing interests** MFK received personal fees from Bristol-Myers Squibb and Celltrion, unrelated to this manuscript. AHK received personal fees from Exagen Diagnostics, Inc and GlaxoSmithKline, unrelated to this manuscript. PMM received personal fees from Abbvie, Eli Lilly, Novartis and UCB Pharma. JY received personal fees from Astra Zeneca and Eli Lilly, unrelated to this manuscript. PCR reports personal fees from Abbvie, Pfizer, UCB Pharma, Novartis, Eli Lilly and Janssen, and non-financial support from Roche.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.



► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2020-217690).



**To cite** Konig MF, Kim AHJ, Scheetz MH, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2020-217690

Received 21 April 2020
Revised 25 April 2020
Accepted 27 April 2020

*Ann Rheum Dis* 2020;**0**:1–2. doi:10.1136/annrheumdis-2020-217690

**ORCID iDs**
Maximilian F Konig http://orcid.org/0000-0001-5045-5255
Alfred HJ Kim http://orcid.org/0000-0003-4074-0516
Pedro M Machado http://orcid.org/0000-0002-8411-7972
Philip C Robinson http://orcid.org/0000-0002-3156-3418

## REFERENCES

1 AHJ K, Sparks JA, Liew JW, *et al*. A rush to judgment? rapid reporting and dissemination of results and its consequences regarding the use of hydroxychloroquine for COVID-19. *Ann Intern Med* 2020:M20–1223.
2 Lane JCE, Weaver J, Kostka K, *et al*. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. *Rheumatology* 2020.
3 Roden DM, Harrington RA, Poppas A, *et al*. Considerations for drug interactions on QTc in exploratory COVID-19 (coronavirus disease 2019) treatment. *J Am Coll Cardiol* 2020. doi:10.1016/j.jacc.2020.04.016. [Epub ahead of print: 09 Apr 2020].
4 Chorin E, Dai M, Shulman E, *et al*. The QT interval in patients with SARS-CoV-2 infection treated with Hydroxychloroquine/Azithromycin. *Cardiovascular Medicine* 2020.
5 Chen Z, Hu J, Zhang Z, *et al*. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *Epidemiology* 2020.
6 Joob B, Wiwanitkit V. Sle, hydroxychloroquine and NO SLE patients with covid-19: a comment. *Ann Rheum Dis* 2020:annrheumdis-2020-217506.
7 Remarks by President Trump, Vice President Pence, and Members of the Coronavirus Task Force in Press Briefing. The white house. Available: https://www.whitehouse.gov/briefingsstatements/remarks-president-trump-vice-president-pence-members-coronavirus-task-forcepress-briefing-19/ [Accessed 24 Apr 2020].
8 Monti S, Montecucco C. Can hydroxychloroquine protect patients with rheumatic diseases from COVID-19? Response to: 'Does hydroxychloroquine prevent the transmission of COVID-19?' by Heldwein and Calado and 'SLE, hydroxychloroquine and no SLE patients with COVID-19: a comment' by Joob and Wiwanitkit. *Ann Rheum Dis*;2020:annrheumdis2020-217524.
9 Gianfrancesco MA, Hyrich KL, Gossec L, *et al*. Rheumatic disease and COVID-19: initial data from the COVID-19 global rheumatology alliance provider registries. *Lancet Rheumatol* 2020:S2665991320300953.
10 Mathian A, Mahevas M, Rohmer J, *et al*. Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine. *Ann Rheumat Dis* 2020. [Epub ahead of print: 24 Apr 2020].
11 Search of: Recruiting, Completed Studies | COVID | Hydroxychloroquine - List Results - ClinicalTrials.gov. Available: https://clinicaltrials.gov/ct2/results?cond=COVID&intr=Hydroxychloroquine&Search=Apply&re crs=a&recrs=e&age_v=&gndr=&type=&rslt= [Accessed 19 Apr 2020].
12 Dyall J, Gross R, Kindrachuk J, *et al*. Middle East respiratory syndrome and severe acute respiratory syndrome: current therapeutic options and potential targets for novel therapies. *Drugs* 2017;77:1935–66.
13 Dyall J, Coleman CM, Hart BJ, *et al*. Repurposing of clinically developed drugs for treatment of middle East respiratory syndrome coronavirus infection. *Antimicrob Agents Chemother* 2014;58:4885–93.
14 Yao X, Ye F, Zhang M, *et al*. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020:ciaa237.
15 Liu J, Cao R, Xu M, *et al*. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020;6:16.
16 Tuntland T, Ethell B, Kosaka T, *et al*. Implementation of pharmacokinetic and pharmacodynamic strategies in early research phases of drug discovery and development at Novartis Institute of biomedical research. *Front Pharmacol* 2014;5:174.
17 Barnard DL, Day CW, Bailey K, *et al*. Evaluation of immunomodulators, interferons and known in vitro SARS-coV inhibitors for inhibition of SARS-coV replication in BALB/c mice. *Antivir Chem Chemother* 2006;17:275–84.
18 CENTER FOR DRUG EVALUATION AND RESEARCH. APPLICATION NUMBER:021246Orig1s045 and 021087Orig1s062 [Abstracted from NDA 21087/S-062 Clinical Review, T. Vargas-Kasambira]. Available: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/021246Orig1s045_021087Orig1s 062SumR.pdf [Accessed 19 Apr 2020].
19 Rayner CR, Bulik CC, Kamal MA, *et al*. Pharmacokinetic-Pharmacodynamic determinants of oseltamivir efficacy using data from phase 2 inoculation studies. *Antimicrob Agents Chemother* 2013;57:3478–87.
20 Arnold SL, Buckner F. Hydroxychloroquine for treatment of SARS-CoV-2 infection? improving our confidence in a model-based approach to dose selection. *Clin Transl Sci* 2020. doi:10.1111/cts.12797. [Epub ahead of print: 08 Apr 2020].
21 Petri M, Elkhalifa M, Li J, *et al*. Hydroxychloroquine blood levels predict hydroxychloroquine retinopathy. *Arthritis Rheumatol* 2020;72:448–53.
22 Tang W, Cao Z, Han M, *et al*. Hydroxychloroquine in patients with COVID-19: an openlabel, randomized, controlled trial. *Infectious Diseases* 2020.