# Is there a future for hydroxychloroquine/chloroquine in prevention of SARS-CoV-2 infection (COVID-19)?

In a recent article, Spinelli *et al* discussed a potential role of antimalarials in prevention of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and suggest that, waiting for supportive data from clinical trials, the scientific community is moving towards pre-emptive use of chloroquine (CQ) and hydroxychloroquine (HCQ).[1]

During pandemic of COVID-19, physicians face an imperative to use the drugs with unproven clinical efficacy and at best only moderate activity against SARS-CoV-2 (CQ and HCQ among them) in an attempt to save lives of patients with severe viral pneumonia complicated by acute respiratory distress syndrome. Several reports from China showed that both CQ and HCQ can block viral replication in vitro,[2 3] whereas a small non-randomised trial from Gautret *et al* found HCQ to have a promising efficacy in enhancing viral clearance.[4] These preliminary data resulted in a widespread use of antimalarials to treat COVID-19 and prompted US President Donald Trump to tout HCQ as 'one of the biggest game-changers in the history of medicine'. However, recent evidence suggests that it might be not true. A small but randomised study from China in patients with mild to moderate COVID-19 treated with HCQ or placebo found no difference in recovery rates,[5] and French investigators failed to confirm antiviral activity or clinical benefit of the HCQ and azithromycin combination in 11 hospitalised patients with severe COVID-19.[6] Moreover, various methodological flaws of Gautret *et al*'s study that may affect the validity of the findings should be also considered, even in the current setting when patients with critical illness should be treated immediately and cannot wait for the results of adequate clinical trials.[7]

Apparently, new data, also inconclusive and equivocal, will not impact the existing practice of using HCQ/CQ to treat patients with moderately severe to severe COVID-19 given a lack of agents with established antiviral efficacy and safety. Moreover, we are already facing expansion of indications for HCQ/CQ administration to include prevention of SARS-CoV-2 infection or postexposure prophylaxis, although these indications are not supported by any data. Of note, in the randomised, double-blind, placebo-controlled trial, prophylaxis with CQ did not prevent influenza despite the drug in vitro activity against virus.[8] Potential side effects of HCQ and CQ, such as retinopathy, vomiting, diarrhoea and prolongation of QT interval with increased risk of arrhythmia, should be also taken into account.[9]

Currently, HCQ and CQ are under investigation in several randomised clinical trials for pre-exposure or postexposure prophylaxis of SARS-CoV-2 infection, including COPCOV (UK, n=40 000), ALBERTA HOPE (Canada, n=1660), COVIDAXIS (France, n=600), PATCH (USA, n=400), NCT04333225 (USA, n=360), NCT04318444 (USA, n=1600), NCT04328961 (USA, n=2000), HYCOVID (France, n=1300) and NCT04328467 (USA, n=3500). Is it really necessary to conduct similar large-scale trials across the world? Is it worthwhile to start testing the drug in thousands or even dozens of thousands of patients without positive results of smaller studies? Only few of the aforementioned trials have already started recruiting patients. Therefore, we can assume that some, if not all, studies will be completed after the pandemics of COVID-19 would hopefully abate. One potential reason explaining the rush is that both sponsors and investigators are eager to provide antimalarials for off-label use in healthcare workers or other individuals at significant risk of infection.

A major consequence of widespread use of HCQ/CQ for treatment and prevention of COVID-19 is a shortage of antimalarials for patients with rheumatic diseases (ie, systemic lupus erythematosus) in whom these medications have established efficacy.[7] For example, HCQ or CQ is currently not available in all Moscow pharmacies. The American College of Rheumatology and several other major medical organisations issued a joint statement warning of possible consequences of shortage of HCQ/CQ and demanding to preserve access to these medications for those patients whose lives and productivity depend on them.[10] Among potential measures, organisations representing patients and physicians recommended to communicate accurate information about antimalarial drugs, their critical role in treatment for the approved indications and the up-to-date status of their use for COVID-19, and to implement restrictions in order to minimise unnecessary prescribing or stockpiling of HCQ/CQ solely for use in COVID-19.

Spinelli *et al* ask whether it is ethical to propose antimalarials for preventing the spreading of SARS-CoV-2 without any evidence-based data. Many physicians caring for patients with severe COVID-19 would probably avoid definite answer in the current setting when millions of people hear frightening statistics, whereas any positive data are rapidly disseminated by the lay press and social media. During evolving pandemics of COVID-19, even the fact that antimalarials are under investigation in many countries can be regarded as 'evidence' by many individuals, not excluding healthcare professionals. We cross our fingers waiting for the results of clinical trials. However, we should not forget our patients with rheumatic diseases who should have timely access to the medications and care on which they have relied for decades.[10]

**Sergey Moiseev** ,[1] **Sergey Avdeev,**[2] **Michail Brovko,**[1] **Pavel Novikov,**[1] **Victor Fomin**[3]

[1]Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia
[2]Clinic of Pulmonology, Sechenov First Moscow State Medical University, Moscow, Russia
[3]Vinogradov Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

**Correspondence to** Professor Sergey Moiseev, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow 119435, Russia; avt420034@yahoo.com

**Contributors** All authors participated in preparing the manuscript and provided their comments.

**Funding** The Russian Academic Excellence Project 5-100

**Competing interests** None declared.

**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; internally peer reviewed.

**To cite** Moiseev S, Avdeev S, Brovko M, *et al*. *Ann Rheum Dis* 2021;**80**:e19.

Received 10 April 2020
Accepted 15 April 2020
Published Online First 21 April 2020


► http://dx.doi.org/10.1136/annrheumdis-2020-217636

*Ann Rheum Dis* 2021;**80**:e19. doi:10.1136/annrheumdis-2020-217570

**ORCID iD**
Sergey Moiseev http://orcid.org/0000-0002-7232-4640

## REFERENCES

1 Spinelli FR, Ceccarelli F, Di Franco M, *et al*. To consider or not antimalarials as a prophylactic intervention in the SARS-CoV-2 (Covid-19) pandemic. *Ann Rheum Dis* 2020;79:666–7.
2 Wang M, Cao R, Zhang L, *et al*. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269–71.
3 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. doi:10.1093/cid/ciaa237. [Epub ahead of print: 9 Mar 2020].
4 Gautret P, Lagier J-C, 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;105949:105949.
5 Chen J, Liu D, Liu L, *et al*. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ* 2020;49.
6 Molina JM, Delaugerre C, Le Goff J, *et al*. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Médecine et Maladies Infectieuses* 2020:S0399-077X(20)30085-8.
7 AHJ K, Sparks JA, Liew JW, *et al*. COVID-19 global rheumatology alliance. 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;30.
8 Paton NI, Lee L, Xu Y, *et al*. Chloroquine for influenza prevention: a randomised, double-blind, placebo controlled trial. *Lancet Infect Dis* 2011;11:677–83.
9 Chorin E, Dai M, Shulman E, *et al*. The QT interval in patients with SARS-CoV-2 infection treated with hydroxychloroquine/azithromycin. *MedRxiv* 2020.
10 Available: www.lupus.org/s3fs-public/pdf/Joint-Statement-on-HCQ-LFA-ACR-AADA-AF.pdf