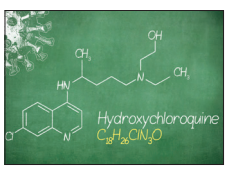
Hydroxychloroquine in the prevention of COVID-19 mortality



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Published Online
November 5, 2020
https://doi.org/10.1016/S2665-9913(20)30390-8

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COVID-19 has affected tens of millions of individuals across the globe and upended the lives of countless others. Despite advances in supportive care and treatment, mortality remains high, and prevention of infection continues to be crucial.[1] Early on in the pandemic, hydroxychloroquine was suggested as a possible prevention method or treatment for COVID-19, given evidence of in-vitro inhibition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[2] propelling this mainstay treatment of rheumatic diseases to prominence and controversy. However, multiple high-quality studies subsequently showed no benefit of hydroxychloroquine use as post-exposure prophylaxis[3] or as a COVID-19 treatment.[4,5] As enthusiasm for hydroxychloroquine as a treatment of SARS-CoV-2 infection rapidly declined, the possibility of the use of this medication to prevent COVID-19 remained, with multiple randomised clinical trials designed to address this possibility. Furthermore, with the spotlight shone on hydroxychloroquine with regards to COVID-19, patients with rheumatic diseases and their care providers have been highly interested as to whether this commonly used medication for systemic lupus erythematosus and rheumatoid arthritis could protect against adverse outcomes of COVID-19.

In *The Lancet Rheumatology,* Christopher Rentsch and colleagues address whether hydroxychloroquine use before SARS-CoV-2 infection could prevent mortality from COVID-19.[6] They did a population-based cohort study using the OpenSAFELY platform, an electronic health records database capturing 40% of the population of England. They included 30 569 patients with systemic lupus erythematosus or rheumatoid arthritis who were already taking hydroxychloroquine in the 6 months before what was considered as the start of the pandemic in England and 164 068 patients with these rheumatic diseases who did not use hydroxychloroquine.[6] Their primary outcome was COVID-19 mortality per death certificate data, and they used cause-specific cox regression models, adjusting for age, sex, ethnicity, geographical region, and other immunosuppressive drugs (ie, other conventional synthetic disease-modifying rheumatic drugs [DMARDs] and oral corticosteroids). The study found no significant difference in standardised cumulative COVID-19 mortality associated with hydroxychloroquine use (0·23% among hydroxychloroquine users and 0·22% among non-users) with an adjusted hazard ratio of 1·03 (95% CI 0·80–1·33). The findings were similar in an extended analysis additionally adjusting for established or suspected risk factors for COVID-19 mortality. Additionally, no difference was seen in non-COVID-19 mortality associated with hydroxychloroquine use.

These findings are not surprising given the mounting body of literature suggesting no clinical benefit for hydroxychloroquine use against COVID-19. However, this study is important in addressing the potential role, or lack thereof, for hydroxychloroquine as a preventive medication for this novel infectious disease. This observational study is the largest, to our knowledge, to address this issue thus far. With an astute approach, this methodologically rigorous study took advantage of a natural experiment by identifying a large cohort of patients with systemic lupus erythematosus and rheumatoid arthritis with pre-pandemic hydroxychloroquine use and their non-user comparators with the same underlying rheumatic diseases. Although this methodological approach and the study's pre-pandemic timeline of hydroxychloroquine exposure helped to minimise confounding by indication, the primary limitations of the study are similar to those of all non-randomised observational studies, in that there could be potential bias between the treatment and comparator groups. There might be unmeasured differences between patients with systemic lupus erythematosus or rheumatoid arthritis who did and did not use hydroxychloroquine, and detailed information about the rheumatic diseases were not known. Furthermore, this study did not account for the use of biologic DMARDs, which have a yet unresolved effect on COVID-19 outcomes.[7] Reassuringly, in sensitivity analyses, the potential effect of these biologics was not found to change the study findings.

The results from this study are consistent with two randomised clinical trials of hydroxychloroquine for pre-exposure prophylaxis in health-care workers at risk of SARS-CoV-2 infection. In these studies,[8,9] health-care workers were randomly assigned to take hydroxychloroquine for 8 weeks or 12 weeks. In both studies, no difference was seen in the risk of SARS-CoV-2 infection associated with hydroxychloroquine use. In the context of these trials, this large cohort study adds new information on the absence of benefit of hydroxychloroquine in

preventing mortality from COVID-19 and addresses the effect of hydroxychloroquine use on COVID-19 outcomes among long-term users with rheumatic diseases. Along with these randomised controlled trials, this study provides important evidence that hydroxychloroquine does not prevent COVID-19.

For rheumatologists and our patients, hydroxychloroquine maintains its important, longstanding role in the treatment of rheumatic diseases, with known benefits ranging from reducing lupus disease activity and damage to lowering the risks of hyperglycaemia, hyperlipidaemia, and pregnancy complications.[10] However, available evidence does not support the use of this medication in the prevention or treatment of COVID-19.

I declare no competing interests.

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Tofacitinib monotherapy in psoriatic arthritis—what is missing?

Published **Online** November 16, 2020 https://doi.org/10.1016/S2665-9913(20)30395-7

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Psoriatic arthritis has a reported incidence of 0·05–0·25% worldwide.[1] Although there are multiple medications approved for treatment of this systemic disease, there are limited oral options which have been shown to effectively treat the multiple domains of psoriatic arthritis effectively.

In *The Lancet Rheumatology,* Peter Nash and colleagues[2] present an interesting and clinically important analysis, albeit in a relatively small number of patients, indicating that tofacitinib monotherapy might be effective in the treatment of patients with psoriatic arthritis. A blinded, randomised clinical trial investigating tofacitinib monotherapy in psoriatic arthritis has not been previously reported.

Nash and colleagues' Article reports a substudy of a long-term extension study of tofacitinib in patients with psoriatic arthritis, in which patients with well controlled disease on a combination of tofacitinib and methotrexate were randomised (1:1) to either continue combination treatment or switch to tofacitinib monotherapy (5 mg twice daily). The co-primary outcomes of the study were change from baseline in psoriatic arthritis disease activity score (PASDAS) and health assessment questionnaire-disability index (HAQ-DI) after 6 months. On the basis of this analysis, the authors correctly conclude that there are some patients who might maintain benefit with tofacitinib monotherapy providing they had been on a stable combination of tofacitinib and methotrexate and had maintained a stable disease state for a considerable amount of time (2 years in this analysis) prior to methotrexate withdrawal.[2]

There are, however, several aspects of this manuscript that require careful attention of the reader.

First, as pointed out by the authors, the 2019 EULAR recommendations[3] for the treatment of psoriatic arthritis state that the optimum dose of methotrexate should