Festina lente: hydroxychloroquine, COVID-19 and the role of the rheumatologist

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As of the end of March 2020, the COVID-19 pandemic has resulted in over 850 000 confirmed cases and an estimated 42 000 deaths worldwide.[1] All agree that safe and effective therapies for treatment and prevention are urgently needed. In the midst of this rapidly progressing crisis, evidence has emerged suggesting that antimalarial medications, such as hydroxychloroquine (HCQ), may be efficacious for COVID-19 treatment. After amplification from politicians, news outlets and social media, a rush to acquire supplies of HCQ resulted in worldwide shortages. Recent government policies may have exacerbated these issues, where wider use in both COVID-19 treatment and prevention were authorised or recommended by India, the US Food and Drug Administration and other countries.[2–4] In response to dwindling supplies, several US states have issued restrictions on HCQ use including limiting dispensation quantities and verifying indications.[5–8] Rheumatologists, researchers and patient partners must advocate for the appropriate distribution and use of HCQ, as millions of people with rheumatic diseases worldwide depend on HCQ to control disease activity and maintain quality of life. In doing so, we must also remind ourselves to 'make haste slowly' (*festina lente*).

Emanuel *et al*[9] published a well-timed commentary suggesting the following principles for fairly allocating scarce resources during the COVID-19 crisis: equal treatment, attempts to maximise benefits and prioritising the most vulnerable. These recommendations echo prior guidance published in 2016 by the WHO on how to address future infectious disease outbreaks.[10] The report cautioned that 'special attention should be given to ensuring that persons who face heightened susceptibility to harm or injustice during infectious disease outbreaks are able to contribute to decisions about infectious disease outbreak planning and response'. This ethical framework offers health systems a structure for approaching the use and distribution of HCQ during the COVID-19 pandemic to minimise potential impact on patients with rheumatic disease.

CONSIDER EQUITY

Allowing a 'first come, first serve' system during an international infectious disease crisis has likely led to disparities in access to HCQ. These deficits have left patients with rheumatic disease who require HCQ to prevent morbidity and mortality in a uniquely vulnerable position. Moreover, we should note that poor outcomes in the rheumatic disease community disproportionately affect populations already facing barriers to healthcare access.[11] For example, patients living in rural areas or those with lower socioeconomic status may not have the additional resources needed to obtain HCQ if not available at their local pharmacy. Thus, disadvantaged patients and those who are underinsured/uninsured are most susceptible to detrimental outcomes as an unintended consequence of COVID-19-related HCQ shortages. Instead of prioritising access based on demonstrated need or an adequate assessment of risk, empiric use in the pandemic has occurred without protecting a sufficient supply for continued use in people with rheumatic disease.

MAXIMISE UTILITY

Decades of research support the use of HCQ in rheumatic diseases. As a particularly notable example, HCQ use in systemic lupus erythematosus (SLE) reduces disease activity,[12] limits damage accrual[13] and improves survival.[14] In a well-designed placebo-controlled randomised trial, discontinuation of HCQ in patients with stable SLE increased the frequency of disease flares.[15] HCQ is also approved by multiple agencies as a treatment option for rheumatoid arthritis (RA), where meta-analyses suggest unique benefits to improve cardiovascular risk, the major cause of excess mortality in these patients.[16]

The evidence supporting HCQ use in COVID-19 is less compelling. In a small non-randomised pilot trial including 26 people with COVID-19 initially treated with HCQ (and azithromycin (AZM) in an additional subset), nasopharyngeal viral clearance at day 6 of treatment was reported in 57% of the 14 patients retained in the analysis who received HCQ monotherapy versus 13% of controls.[17] However, concerns about the study design and data analysis have been previously discussed,[18] and a potential signal toward increased harm in patients treated with HCQ cannot be dismissed outright. Since then, another preprint by Gautret *et al* described a selected cohort of 80 patients with COVID-19.[19] Rather than lending clarity to the ongoing debate,

this has created more confusion. Almost all (92%) of COVID-19 subjects examined had mild disease, and four patients were asymptomatic carriers. Such a study population would seem likely to have favourable clinical outcomes and early viral clearance, regardless of intervention. The absence of a control group also precludes analysis of any potential harm related to HCQ's experimental use in these patients.

Two subsequent randomised controlled trials have similarly provided insufficient clarification. An open-label randomised controlled trial of 30 patients recently reported no significant differences in viral clearance between a group receiving HCQ (13 out of 15, 87%) and a group receiving standard of care (14 out of 15, 93%).[20] On the contrary, another single-centre, double-blind, randomised parallel-group trial suggested improvements in clinical outcomes (fever, cough) and pulmonary CT findings in those receiving HCQ versus placebo and usual care.[21] This trial also suffered from inconsistencies in its study protocol, inadequate primary outcome measures, a small sample size and inappropriate statistical methodology (eg, since power calculations to justify the reported sample size were not performed, the p-values are difficult to interpret).

Fortunately, more rigorously designed randomised controlled trials with adequate power to assess meaningful outcomes for the prophylaxis and treatment of COVID-19 are underway (eg, NCT04307693, NCT04323631, NCT04315896). These trials will also provide safety profiles of these therapies when used for COVID-19. Both HCQ and AZM are known QTc prolonging agents. Their combined administration in a novel disease where cardiomyopathy and cardiac arrhythmias have been reported, even in not-critically ill patients,[22] warrants further investigation before widespread use can be recommended. While the evidence supporting HCQ use in rheumatic diseases is scientifically established and validated in numerous studies, the evidence for its use in the treatment of COVID-19 remains limited.

PROTECT VULNERABLE PATIENTS

According to the 2016 WHO ethical guidelines, 'Even when public health measures are designed with the best of intentions, they can inadvertently place a disproportionate burden on particular populations'. As empiric use for HCQ in COVID-19 has been widely taken up, this inadvertently leaves patients with rheumatological conditions vulnerable to medication shortages. Until HCQ production can meet the new demands and data supporting its use are more certain, we should determine whether patients with rheumatological diseases, where efficacy and safety are established, should be given priority over individuals who receive HCQ for use as pre-exposure or post-exposure prophylaxis. Patients with rheumatic disease are at particular risk of worsening disease if they lose access to HCQ. Flares may require emergency visits or hospitalisations in an already overburdened medical system, which exposes an immunosuppressed patient population to an increased risk of acquiring COVID-19. This is not just a theoretical risk but was observed with Middle East respiratory syndrome.[23] Moreover, treatment with more potent immunosuppressant medications in lieu of HCQ, such as glucocorticoids, may increase the risk of severe complications from COVID-19 infection. Thus, HCQ overutilisation related to COVID-19 treatment may jeopardise the health of patients with rheumatic diseases.

Given this framework, we support the guiding principles recently published by the American College of Rheumatology.[24] These include allocating adequate supplies to people with SLE and RA and exempting patients with other rheumatic conditions from utilisation management practices.

At this time, ballooning infection rates threaten to overwhelm the capacity of healthcare systems worldwide. Safe and effective therapies for COVID-19 are desperately needed. We, like many physicians, hope well-designed studies will demonstrate HCQ's efficacy against COVID-19 infection. In the meantime, provisions should be underway to ensure adequate supply for all indications, particularly our patients with rheumatic diseases. Until such evidence emerges, as rheumatologists we must advocate for individuals in whom the safety and efficacy of HCQ is established. Lastly, we recognise that fair resource allocation ultimately depends on separation of responsibilities. While it is our duty to advocate for our patients, it is also our responsibility to respect the difficult decisions made by the larger medical and patient communities in these uncertain times.

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