

The Journal of Rheumatology

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DOI: 10.3899/jrheum.200369

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Hydroxychloroquine: a potential ethical dilemma for rheumatologists during the COVID-19 pandemic

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Category: Editorial

No funding was provided for this manuscript

Conflict of interest: RS, ES and MAF reports no conflict of interest

All authors participated in the writing of this manuscript

Running head: Hydroxychloroquine during COVID-19 pandemic

Key indexing terms: hydroxychloroquine, COVID-19, rheumatic diseases, ethics

Two antimalarial agents, chloroquine (CQ) and hydroxychloroquine (HCQ), have been trusted treatments for a range of rheumatic diseases over the past seventy years [1]. These agents have attracted intense media attention in the past few weeks with suggestions that this category of drugs may have potential in the management of coronavirus (SARS-CoV2) associated disease called COVID-19 [2, 3]. In this unprecedented time of a world viral pandemic that is associated with considerable mortality, rheumatologists can anticipate challenges in clinical care. We must counsel patients about the appropriate use of HCQ (since CQ is not currently available in Canada) in management of rheumatic diseases, provide valid scientific information regarding the current evidence for effect in COVID-19 disease and be poised to provide alternate drug treatment in the event that HCQ may be allocated away from routine rheumatology clinical care to treat seriously-ill viral-infected patients. These issues are pertinent and imminent for the rheumatologist and require an understanding of the current available knowledge, and consideration of a possible ethical dilemma in the event that drug supply is limited.

History of Antimalarial Therapy

Antimalarial therapy began in the mid 17th century with observations by Jesuit missionaries in Peru that the bark of a specific tree, later named *Cinchona*, could be used to treat the severe febrile illness now known to be malaria [4]. In the late 17th century, the Peruvian bark, mixed with rose leaves, lemon juice and wine was a widely used secret treatment for fever in the malarious regions of England [4]. Quinine is a complex structured alkaloid and the active therapeutic component of the *Cinchona* tree. It was isolated and named in 1820 by two French chemists, Pelletier and Caventou [4]. Until the 1850s all the cinchona bark came from the wild forests of the Andean republics of South America leading to world market competition. Having secretly acquired seeds and saplings from South America, botanists from Kew Gardens worked with botanical gardens in India and Java to develop hybrid species of the *Cinchona* tree for plantations in Java, which became the main source of quinine [4]. Following World War I, when German troops were unable to access quinine from Java, German chemists produced a synthetic version of quinine in the early 1930's named mepacrine [4]. Mepacrine was subsequently also produced in the United States (US). Enemy propaganda during World War II spread the message that mepacrine would cause yellow skin discoloration as well as infertility, resulting in mass discontinuation of malaria prophylaxis by US troops in the Far East [4]. In an effort to stem the tide of malaria infections in US troops, US chemists synthesized CQ, a chemical variant of quinine, another synthetic antimalarial produced in Germany [4].

Antimalarials as a Rheumatic Disease Treatment

During World War II, there were serendipitous observations of improved autoimmune skin disease and arthritis associated with CQ use [5]. Toxicity related to CQ was reduced when HCQ was developed by the addition of a β -hydroxy chain to the CQ molecule [6]. By the 1950's, reports were emerging of the clinical use of CQ and HCQ in the management of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [7-9]. One such report in 1957 was by a Vancouver physician, Dr. Bagnall, who reported on a four-year study of the use of CQ in 125 RA patients who were "carefully followed up personally" [8]. With positive results in 70% of patients, Dr. Bagnall reported on the absence of "definite serious toxic effects" but did concede that there were minor toxic reactions. He also stated that there was a latent period of up to 3 months before effect, with maximum benefit for some delayed for as long as 6-12 months, leading to the statement that short duration treatment was of no value [8].

Thereafter, both CQ and HCQ were identified as disease modifying anti-rheumatic drugs (DMARD), with use continuing into the 21st century. With the emergence of additional synthetic DMARDs, and in recent

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times the biologic DMARDs, there has likely been a reduction in use of HCQ for patients with RA in particular; but HCQ remains a mainstay of treatment for an array of rheumatic autoimmune diseases, with the most important use in SLE [10, 11]. In a first discontinuation study, Esdaile and colleagues demonstrated that stopping HCQ in patients with stable SLE resulted in over twice the risk of having a disease flare [12]. This small pivotal study of 47 patients with stable SLE has promoted the current treatment practice, supported by guidelines worldwide, to maintain patients with SLE on HCQ indefinitely, even if disease severity requires introduction of more vigorous immunosuppressive treatments [13-15]. HCQ has proved invaluable in the management of skin manifestations of SLE as well as other immunological related skin disorders [16]. There are more wide reaching effects of HCQ with recent study reporting attenuation of polyautoimmunity in patients with SLE [17]. In a nationwide Spanish study of 3679 SLE patients with 13.6% having polyautoimmunity (comorbid autoimmune thyroiditis, RA, scleroderma, inflammatory myopathy and mixed connective tissue disease), antimalarial drugs were associated with a lower risk of polyautoimmunity [OR (95% CI), 0.50 (0.38, 0.67)] [17]. An important advantage of HCQ is safety in pregnancy, first reported by Hughes and colleagues in the United Kingdom in 1992 [18]. In a study of 100 pregnancies in patients with SLE, specifically addressing fetal loss related to circulating antiphospholipid antibodies, no fetal malformations were associated with HCQ use [18]. With three decades of study and clinical experience, HCQ has become one of the mainstays in controlling numerous immune conditions in pregnancy without fetal risk [19, 20].

Mechanism of Action and Recent Studies of CQ and HCQ in COVID 19

CQ and HCQ have in vitro potential to reduce activity of SARS-CoV-2 [2]. They are weak bases that accumulate preferentially in the acidic environment of lysosomes and phagolysosomes with ability to block virus infectivity by raising endosomal pH, causing interference with virus/cell fusion and also interfering with glycosylation of cellular receptors of SARS-CoV. Therefore, CQ and HCQ function at both the viral entry and post-entry stages of infection [2, 3].

Given these in vitro effects, a number of clinical trials were rapidly initiated in China to test the efficacy and safety of CQ in COVID-19 associated pneumonia. Gao and colleagues have reported early preliminary findings on more than 100 patients that CQ was superior to placebo in reducing pneumonia exacerbation, duration of illness and duration of clearance of virus [21]. This report must be viewed as extremely preliminary with minimal information regarding methodology and analysis of data provided. Even so, with these early results, the National Health Commission of the People's Republic of China has included CQ in recommendations regarding management of COVID-19 pneumonia [22]. Colson and colleagues have suggested that HCQ, which has a similar mechanism of action as chloroquine, could be equally effective with a suggested dosage of 600 mg/day in order to reach serum concentrations of 1µg/ml [2, 23]. These researchers published a small non-randomized study of 36 of 42 hospitalized patients who met inclusion criteria. Twenty-six received active treatment with a total 600 mg/day of HCQ for 10 days. Six of these 26 also received azithromycin (500 mg for 1 day then 250 mg/day for 4 days) to prevent bacterial superinfection. Sixteen control patients did not receive these active treatments. Six of the HCQ patients discontinued treatment early: 3 patients were transferred to the intensive care unit (ICU), one died at day 3, one was lost to follow up and another stopped due to nausea. No control patients were lost to follow-up. At day 6, of the 20 remaining treated patients, 100% of HCQ/azithromycin, 57.1% HCQ only and 12.5% of the control group showed nasopharyngeal clearance of virus [24]. There are considerable limitations to this study: 1) the sample size was small; 2) the control group was recruited from other centers; 3) deaths (1 patient) and ICU admissions (3 patients) occurred early in the treatment group, and without clinical outcomes reported for the control group; 4) treatment was not consistent for the active group [24].

Ethical Questions in the Care of Rheumatology Patients

In this rapidly evolving health context, rheumatologists find themselves placed as the most common prescribers of an "old" drug that may have potential to be a lifesaver in this catastrophic era of a viral pandemic. Although in vitro studies of antimalarials and SARS-CoV2 are promising and have a mechanistic

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explanation, the clinical evidence at this time is lacking and must be seen as anecdotal. Rheumatologists are not the gatekeepers for access to HCQ, but some ethical issues require consideration. It is paramount that continued clinical care of patients with chronic diseases such as SLE and inflammatory arthritis who require HCQ maintenance treatment must proceed. Discontinuation of HCQ could lead to disease flare with significant morbidity and even mortality in patients with SLE. The safety of pregnant patients with rheumatic diseases requiring treatment with HCQ must be strongly protected.

Anticipating limited availability of HCQ in the coming weeks and months, the question to be asked will be “who should get HCQ treatment?”. Rheumatologists must advocate strongly for continued access to HCQ for valid clinical indications. In addition to SLE, there are many patients with various autoimmune rheumatic diseases including palindromic rheumatism, Sjogren’s syndrome, cutaneous lupus and even milder forms of RA that currently have disease sufficiently controlled with HCQ, not requiring treatment with more complex DMARDs, and should not be denied continued treatment. Other conditions such as osteoarthritis are not an indication for use of HCQ, and should not be prescribed [25]. Rheumatologists must join the scientific community and support the recommendation that any use of HCQ to treat COVID-19 must be limited to the hospital and/or intensive care unit settings within the context of a formal research protocol. Therefore off-label use outside of these settings should be prohibited. As there is no current evidence that HCQ can be used to prevent SARS-CoV2 infection the public should be informed not to seek to self-medicate by requesting a prescription or ‘borrowing’ from a family member for whom it is prescribed legitimately. Importantly, patients should be educated not ever to share their medication. With judicious use, we hope that all with diseases that require HCQ will continue to have access to it and urge producers and suppliers to be proactive in ensuring sufficient supply.

Despite these strategies, and in the event of a limited supply of HCQ, rheumatologists may have to choose which of their patients should remain on HCQ. This ethical decision will be difficult if rheumatologists are forced to take decisions of deprescribing HCQ. Rheumatic disease patients with life-threatening illnesses such as SLE, or pregnant patients must have priority to continue treatment. We will need to examine in which patients with inflammatory arthritis HCQ is less essential. This may particularly apply to those whose disease is well-controlled and may currently be receiving an additional DMARD. Empathetic discussion with a patient in this setting could be framed in the context of a societal contribution towards an overwhelming health disaster, with opportunity to have some influence on outcome for others. Whether this step could truly influence access and supply of HCQ as a potential treatment for this current human catastrophe is unknown. In this unprecedented time, every single effort towards stemming this most awful global event should be made, but with caution to respect and adhere to the tenets of evidence-based medicine.

Acknowledgement: Rosie Scuccimarri is chair of the Canadian Rheumatology Association (CRA) Therapeutics Committee, Evelyn Sutton is president of CRA, Mary-Ann Fitzcharles is past-chair CRA Therapeutic Committee.

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