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Guiding Principles from the American College of Rheumatology for Scarce Resource Allocation During the COVID-19 Pandemic: The Case of Hydroxychloroquine

Background

Ethical principles must be balanced when making decisions about scarce resource allocation. In extreme circumstances, like the COVID-19 pandemic caused by the SARS-CoV-2 virus, the focus of medical care "shifts from the needs of the individual (ethical principle of autonomy) to the needs of the community as a whole (ethical principle of distributive justice)" (1) with the goal of achieving the greatest good for the greatest number of people.

Hydroxychloroquine (HCQ) is an essential medicine for patients with systemic lupus erythematosus (SLE). It is also a mainstay of therapy for many patients with rheumatoid arthritis. In the case of SLE, including pregnant women with SLE, "hydroxychloroquine is the cornerstone of medical therapy.... It should be used in every patient unless there is a clear contraindication. It is the only medication shown to increase survival in lupus patients. It has been shown to reduce lupus flares and prevent organ damage including cardiovascular events (2)." Withdrawal of HCQ from SLE patients for periods as short as two weeks, even in those with previously clinically stable disease, is associated with flares (3, 4).

Hydroxychloroquine has received much attention in the lay and scientific press as the COVID-19 pandemic has evolved. Chloroquine and hydroxychloroquine, among other agents (5), have demonstrated antiviral activity against SARS-CoV-2 in tissue culture (6-8). These findings, as well as the relative tolerability of HCQ in patients taking the drug for its traditional FDA-approved indications, raised interest in these agents as potential therapeutic options in the current COVID-19 pandemic.

A high-profile report by Gautret, *et al*. (9) describing the use of HCQ alone and in combination with azithromycin in patients with COVID-19 was made public on 17 March 2020. HCQ and azithromycin were subsequently promulgated as therapeutic options for patients with COVID-19 by President Trump and other government officials starting with a press conference on 19 March 2020. Serious flaws in the methodology and interpretation of the data in the Gautret paper were quickly publicized (10, 11).

Shortages of HCQ, a drug with relatively few regular manufacturers and a history of shortages and price spikes in the US, were noted before the press conference and became widely reported in the days that followed (12). Subsequently, the FDA issued an emergency use authorization (EUA) for HCQ and chloroquine, allowing these drugs to be donated to the Strategic National Stockpile to be distributed and prescribed by

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doctors to hospitalized patients with COVID-19, as appropriate, when a clinical trial is not available or feasible.

Since then, numerous randomized and observational trials have 1) failed to show a benefit from HCQ in patients hospitalized with COVID-19 or in post-exposure prophylaxis, 2) been halted due to lack of benefit at the time of interim analyses, and/or 3) highlighted concerns about potential cardiotoxicity, particularly when HCQ is used in combination with drugs that prolong the QT interval such as macrolide antibiotics (13-21). One subsequent study suggesting a potential benefit from HCQ was noted to have serious methodologic flaws (22, 23). On 24 April 2020, the FDA issued a warning against the use of HCQ for treatment of COVID-19 outside of clinical trials (24). On 15 June 2020, the FDA revoked HCQ's EUA. Subsequently, several countries have specifically prohibited the use of HCQ in COVID-19 patients (25).

We offer the following recommendations regarding the allocation of HCQ during the COVID-19 pandemic. Clinical guidance from the American College of Rheumatology for the treatment of rheumatology patients during the COVID-19 pandemic are available here. Guidelines from the Infectious Diseases Society of America are here. All recommendations are based on current knowledge and are subject to revision as circumstances evolve.

Recommendations

- The use of HCQ as part of a COVID-19 treatment regimen outside of a clinical trial is NOT recommended.
- In recognition that HCQ prescribing for COVID-19 patients may continue, in spite of the lack of scientific evidence in support of its use, every effort must be made to ensure an adequate supply of HCQ for patients who need it. Protections on the supply of HCQ should include all aspects of the supply chain from manufacturer to wholesaler, wholesaler to pharmacy, and final distribution to patients.
- Adequate supplies of HCQ should be allocated for patients with SLE, especially pregnant SLE patients and those in whom even brief drug holidays would be reasonably expected to cause a flare of their disease or require a switch to an alternative regimen with less efficacy and/or safety.
- In the case of COVID-19, allocation of HCQ should be reserved for use in clinical trials designed to test the efficacy of HCQ as pre-exposure prophylaxis, post-exposure prophylaxis, and therapy both in mild-to-moderate as well as severe cases of COVID-19.
- Such trials should be carried out by experienced investigators equipped to generate and interpret reliable results while safeguarding patient safety and informed consent. The risk of adverse events, including QT prolongation (26), in

critically ill COVID-19 patients receiving HCQ in combination with other drugs underscores the need for HCQ trials to take place in a controlled setting.

- During HCQ shortages we urge insurers to exempt rheumatology patients from prior authorization (PA), step therapy protocols, and other utilization management practices so that they may more readily gain access to appropriate alternatives as determined by their rheumatologist or rheumatology health professional.
- Insurers who have instituted restrictive HCQ access policies during the COVID-19 pandemic (new PA requirements, quantity limits, or limitations on approved ICD-10 codes, for example, when HCQ is frequently, appropriately and effectively used for undifferentiated or other rheumatologic diseases including undifferentiated inflammatory arthritides), should immediately rescind such policies in light of the weight of scientific data refuting the role of HCQ in treatment of COVID-19.
- Importation restrictions on HCQ should be relaxed during the COVID-19 pandemic to create alternative avenues for distribution of HCQ in the US.

To Be Avoided

- Unrestricted access to HCQ for COVID-19 prophylaxis or treatment in the absence of clinical trial data supporting its use is inappropriate.
- Pharmacy-level restrictions on new starts of HCQ for patients with SLE or any rheumatologic indication are inappropriate.
- Predatory price increases or cost-sharing requirements, especially during the COVID-19 pandemic, should be vigorously opposed by regulatory bodies.

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