Hydroxychloroquine for the Prevention of Covid-19 — Searching for Evidence

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), has generated a worldwide pandemic. The interruption of its spread depends on a combination of pharmacologic and nonpharmacologic interventions. Initial SARS-CoV-2 prevention includes social distancing, the use of face masks, environmental hygiene, and hand washing.[1] Although the most important pharmacologic interventions to prevent SARS-CoV-2 infection are likely to be vaccines, the repurposing of established drugs for short-term prophylaxis is another, more immediate option.

Some researchers have promoted chloroquine and hydroxychloroquine for the treatment and prevention of illness from a variety of microorganisms, including SARS-CoV.[2] Hydroxychloroquine can inhibit replication of SARS-CoV-2 in vitro.[3] Some observational studies have suggested benefits of hydroxychloroquine for the treatment of Covid-19, whereas other treatment reports have described mixed results.[4]

Boulware et al. now report in the *Journal* the results of a randomized trial testing hydroxychloroquine as postexposure prophylaxis for Covid-19.[5] This is described by the investigators as a "pragmatic" trial in which participants were recruited through social media and almost all data were reported by the participants. Adults who described a high-risk or moderate-risk exposure to someone with Covid-19 in their household or an occupational setting were provided hydroxychloroquine or placebo (by mail) within 4 days after the reported exposure, and before symptoms would be expected to develop. The authors enrolled 821 participants; an illness that was considered to be consistent with Covid-19 developed in 107 participants (13.0%) but was confirmed by polymerase-chain-reaction assay in less than 3% of the participants. The incidence of a new illness compatible with Covid-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]). Although participant-reported side effects were significantly more common in those receiving hydroxychloroquine (40.1%) than in those receiving placebo (16.8%), no serious adverse reactions were reported.

This trial has many limitations, acknowledged by the investigators. The trial methods did not allow consistent proof of exposure to SARS-CoV-2 or consistent laboratory confirmation that the symptom complex that was reported represented a SARS-CoV-2 infection. Indeed, the specificity of participant-reported Covid-19 symptoms is low,[6] so it is hard to be certain how many participants in the trial actually had Covid-19. Adherence to the interventions could not be monitored, and participants reported less-than-perfect adherence, more notably in the group receiving hydroxychloroquine. In addition, those enrolled in the trial were younger (median age, 40 years) and had fewer coexisting conditions than persons in whom severe Covid-19 is most likely to develop,[7] so enrollment of higher-risk participants might have yielded a different result.

The trial design raises questions about the expected prevention benefits of hydroxychloroquine. Studies of postexposure prophylaxis are

intended to provide an intervention in the shortest possible time to prevent infection. In a small-animal model of SARS-CoV-2 infection,[8] prevention of infection or more severe disease was observed only when the experimental antiviral agent was given before or shortly after exposure. In the current trial, the long delay between perceived exposure to SARS-CoV-2 and the initiation of hydroxychloroquine (≥3 days in most participants) suggests that what was being assessed was prevention of symptoms or progression of Covid-19, rather than prevention of SARS-CoV-2 infection.

Drugs for the prevention of infections must have an excellent safety profile. When hydroxychloroquine was initially promoted as a possible solution to SARS-CoV-2 infection, the safety of the drug was emphasized.[2] Under closer scrutiny, however, the potential for cardiac toxic effects and overall adverse outcomes have been emphasized, especially in persons with underlying coexisting conditions that increase the risk of severe Covid-19.[9] Boulware et al. report frequent mild side effects of hydroxychloroquine, but cardiac toxic effects could not be assessed.

So, what are we to do with the results of this trial? The advocacy and widespread use of hydroxychloroquine seem to reflect a reasonable fear of SARS-CoV-2 infection. However, it would appear that to some extent the media and social forces — rather than medical evidence — are driving clinical decisions and the global Covid-19 research agenda.[10] On June 1, 2020, ClinicalTrials.gov listed a remarkable 203 Covid-19 trials with hydroxychloroquine, 60 of which were focused on prophylaxis. An important question is to what extent the article by Boulware et al. should affect planned or ongoing hydroxychloroquine trials. If postexposure prophylaxis with hydroxychloroquine does not prevent symptomatic SARS-CoV-2 infection (with recognition of the limitations of the trial under discussion), should other trials of postexposure prophylaxis with hydroxychloroquine continue unchanged? Do the participants in these trials need to be informed of these results? Do these trial results with respect to postexposure prophylaxis affect trials of preexposure prophylaxis with hydroxychloroquine, some of which are very large (e.g., the Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine [HERO-HCQ] trial, involving 15,000 health care workers; ClinicalTrials.gov number, NCT04334148)? The results reported by Boulware et al. are more provocative than definitive, suggesting that the potential prevention benefits of hydroxychloroquine remain to be determined.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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