CORRESPONDENCE

Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

TO THE EDITOR: The window for postexposure prophylaxis against Covid-19 is narrow.[1-3] Therapy that is initiated up to 4 days after exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is early treatment, not postexposure prophylaxis. The trial described in the article by Boulware et al. (published online on June 3 at NEJM.org)[4] was therefore largely about the prevention of symptoms in persons who may already have been infected. The trial was designed to detect a 50% relative reduction in new cases of symptomatic Covid-19; this estimate was overly optimistic. The trial was not powered to detect an important, but lesser reduction. Regardless, the authors found a nonsignificant (P=0.35) absolute difference of −2.4 percentage points (a 17% relative reduction) in the incidence of new symptomatic illness compatible with Covid-19 between the percentage of participants who received hydroxychloroquine within 4 days after exposure and those who received placebo. The upper boundary of the 95% confidence interval was an absolute reduction of approximately 7 percentage points (a relative reduction of approximately 50%), which was the investigators' prespecified target effect size.

We can draw three conclusions. First, hydroxychloroquine might be effective in early treatment, since the absence of evidence is not evidence of absence. Second, a larger trial involving participants with a virologic diagnosis should be conducted to detect a meaningful early treatment effect (e.g., a trial involving 8000 participants could detect a reduction in the incidence of symptomatic Covid-19 from 15.0% to 12.5%). Third, other trials examining preexposure prophylaxis and early postexposure prophylaxis should be considered.

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TO THE EDITOR: The primary results of the trial conducted by Boulware et al. were nonsignificant, and the trial was interpreted as negative. A few points warrant careful consideration. First, the reverse fragility index was only 5 (i.e., 5 events would have to change in order for the primary end point to move from nonsignificant to significant). The reverse fragility quotient (the reverse fragility index divided by the sample size) was 0.006, which indicates that the nonsignificance of the results was contingent on only 0.6 events per 100 participants. Second, the absolute risk reduction was 2.4 percentage points. This magnitude of absolute risk reduction is similar to that in other positive trials.[1,2] The number needed to treat was 42, which may be acceptable considering the current escalating pandemic. Third, the trial was powered to detect a 50% relative reduction in new symptomatic infections, which is an extraordinary robust estimate. Therefore, in accordance with the guidelines of the *Journal* and the American Statistical Association, it is critical to not view results in a dichotomized manner on the basis of P values, especially when the results are fragile, the trial is underpowered,

and other statistical measures suggest a possible benefit with no signal for harm.[3,4]

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TO THE EDITOR: The trial by Boulware et al. that showed ineffectiveness of hydroxychloroquine for prevention of Covid-19 nevertheless reestablished the safety of hydroxychloroquine in otherwise healthy persons. The primary conclusions of the trial regarding the ineffectiveness of hydroxychloroquine to protect against Covid-19 rely heavily on the incidence of new illness compatible with Covid-19 (reported in 11.8% of the participants in the hydroxychloroquine group and 14.3% of those in the placebo group) rather than on laboratory-confirmed diagnoses (in only 2.7% and 2.2% of the participants, respectively). Did the participants who had symptoms compatible with Covid-19 also undergo laboratory testing for SARS-CoV-2 infection? It would be important for all 821 asymptomatic participants with high-risk exposure who were enrolled in the trial to undergo testing for SARS-CoV-2 infection before and after the administration of hydroxychloroquine.[1]

Asymptomatic persons with Covid-19 pose a considerable challenge with respect to the hazard of exposure and community spread of SARS-CoV-2 infection.[2] The classification and identification of Covid-19–positive persons on the basis of symptoms may be misleading because of the variable and overlapping symptoms of the disease.[3] The results of the trial conducted by Boulware et al. with respect to the moderate risk of Covid-19 and the low incidence of hospitalizations in a population with high-risk exposure to SARS-CoV-2 are important for disease management.[4]

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THE AUTHORS REPLY: In response to Avidan and colleagues: we agree that the postexposure prophylaxis window for SARS-CoV-2 is narrow; for this reason, we used a pragmatic trial design, and trial medication was shipped overnight to participants (68% of the participants began to receive hydroxychloroquine or placebo within 1 to 3 days). Although Avidan et al. suggest that a trial involving 8000 participants is indicated in order to detect an absolute reduction in symptoms of 2.4 percentage points, our trial was designed to detect a

50% relative reduction in the incidence of symptomatic Covid-19 and was completed in 7 weeks in the setting of a pandemic in order to provide meaningful timely results. It would have been impractical to undertake an unfunded trial that was 10 times as large as our trial. For a therapy to be widely used as postexposure prophylaxis, it should provide a significant reduction in the incidence of infection. For example, preexposure or postexposure prophylaxes against human immunodeficiency virus infection or bacterial meningitis are more than 90% effective.[1,2] We agree that trials evaluating the benefit of hydroxychloroquine as preexposure prophylaxis remain valuable.

In response to Khan and Butler: the reverse fragility index for our trial was 10, which implies that if there was a 20% reduction in the percentage of participants with new Covid-19–compatible illnesses in the intervention group (from 49 to 39 participants), the results would be different (39 of 414 participants in the hydroxychloroquine group and 58 of 407 participants in the placebo group, P=0.04). However, this is not what we found. In this context, we think that widespread use of hydroxychloroquine as postexposure prophylaxis is not warranted.

In response to Tekwani: we agree that classification of participants on the basis of illness compatible with Covid-19 is a limitation, and we acknowledge this limitation in our article. In most locales in March and April 2020, SARS-CoV-2 testing was unavailable to most persons in the United States who were not hospitalized, including 60% of the health care workers in our trial. Thus, we relied on the identification of symptoms consistent with Covid-19 put forth by the Council of State and Territorial Epidemiologists.[3] In a perfect world, polymerase-chain-reaction (PCR) testing would have been preferable; however, even PCR is not perfect for detecting early infections. On the first day of symptoms, false negative PCR results are estimated to occur in 38% of patients (range, 18 to 65), and these false negative results decrease over time.[4] An effective prophylaxis would reduce the incidence of symptomatic disease as well as that of laboratory-confirmed disease. We hope that the scientific community can build on our results with additional, well-designed randomized clinical trials.

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Since publication of their article, the authors report no further potential conflict of interest.

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