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Updates on Hydroxychloroquine in Prevention and Treatment of COVID-19



In the prevention and treatment of Coronavirus disease 2019 (COVID-19) in the United States, 74% trust their health care providers.¹ In 2021 there have been more than 560,000 prescriptions² of hydroxychloroquine for the prevention, post-exposure prophylaxis, and treatment of COVID-19. Last year, the >890,000 prescriptions were ninefold greater than previous years, leading to major shortages for the approved indications of autoimmune diseases.³ Biological mechanisms support inhibition of the virus that causes COVID-19.⁴ Some case series lacking comparison groups, claims databases, and observational studies,³ all of which have confounding by indication, reported possible benefits.^{5,6} Randomized trials published in high-quality

peer-reviewed journals, which provide the most reliable evidence to detect the most plausible small to moderate effects, have shown disappointing results.³⁻⁶

When the totality of evidence is incomplete, it is appropriate for health care providers to remain uncertain.⁵ Nonetheless, regulatory authorities are sometimes compelled to act on incomplete evidence. On March 28, 2020, the US Food and Drug Administration issued an Emergency Use Authorization for hydroxychloroquine in COVID-19. By April 24, 2020, the Food and Drug Administration issued a Drug Safety Communication warning about potentially fatal prolongations of the QTc interval detectable on 12-lead electrocardiograms and risks of other serious cardiac arrhythmias.³

In this Commentary we review the recent major randomized, double-blind, placebo-controlled trials of hydroxychloroquine in post-exposure prophylaxis and hospitalized patients, addressing the primary endpoint of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infections, as well as their meta-analyses. We thus provide updated perspectives on benefits and risks.

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HYDROXYCHLOROQUINE IN POST-EXPOSURE PROPHYLAXIS

One randomized, double-blind, placebo-controlled trial included 821 post-exposure prophylaxis subjects, of whom 107 developed COVID-19 over 14 days. The 49 of 414 (11.8%) assigned hydroxychloroquine and 58 of 407 (14.3%) given placebo resulted in a nonsignificant relative risk (RR) of 0.83 ($P = .35$). Overall, 140 of 349 (40.1%) assigned hydroxychloroquine reported a side effect by day 5, as compared with 50 of 352 (16.8%) assigned placebo, a highly significant increase ($P < .001$). Nausea, loose stools, and abdominal discomfort were the most common, and there were no serious intervention-related adverse effects.⁷

In another study, among 2314 healthy contacts of 672 COVID-19 index cases, 1116 were randomized to hydroxychloroquine and 1198 to usual care. COVID-19 occurred among 5.7% assigned to hydroxychloroquine and 6.2% to usual care, yielding a nonsignificant RR of 0.89 (95% confidence interval [CI], 0.54-1.46). Adverse events were significantly higher in hydroxychloroquine (51.6%) compared

with usual care (5.9%), but there were no reported cardiac arrhythmias.⁸

In the most recently published trial, 671 households were randomly assigned: 337 (407 participants) to hydroxychloroquine and 334 (422 participants) to the control group. By day 14, there were 53 events in hydroxychloroquine and 45 among usual care, yielding a nonsignificant RR = 1.10 (95% CI, 0.73-1.66); $P > .20$). The frequency of participants experiencing adverse events was significantly higher in the hydroxychloroquine group than the control group (66 [16.2%] vs 46 [10.9%]; $P = .026$).⁹

HYDROXYCHLOROQUINE IN HOSPITALIZED PATIENTS

One trial was terminated early by the external, independent Data Monitoring Committee due to lack of efficacy and futility. Death within 28 days occurred in 421 patients (27%) in the hydroxychloroquine group and in 790 (25%) in the usual-care group, yielding a nonsignificant RR = 1.09 (95% CI, 0.97-1.23; $P = .15$). Patients assigned hydroxychloroquine were significantly less likely to be discharged from the hospital alive within 28 days than those in usual care (59.6% vs 62.9%; RR = 0.90; 95% CI, 0.83-0.98). Among the patients not dependent on mechanical ventilation at baseline, those in the hydroxychloroquine group had a significantly higher frequency of invasive mechanical ventilation or death (30.7% vs 26.9%; RR = 1.14; 95% CI, 1.03-1.27). There were no significant differences in new major cardiac arrhythmias.¹⁰

At 405 hospitals in 30 countries, of 11,330 patients, 2750 were assigned to remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to no trial drug. Adherence was 94%-96% midway through treatment, with 2%-6% crossover. Of 1253 deaths reported, 301 were among those assigned to remdesivir and 303 among its control, yielding a nonsignificant RR = 0.95 (95% CI, 0.81-1.11, $P = .50$). Further, there were 104 deaths among those given hydroxychloroquine, and 84 among its control, yielding a nonsignificant RR = 1.19 (95% CI, 0.89-1.59; $P = .23$). There were 148 deaths in patients assigned lopinavir and 146 among its control, yielding a nonsignificant RR = 1.00 (95% CI, 0.79-1.25; $P = .9$). Finally, there were 243 deaths among patients assigned interferon and 216 receiving its control, yielding a nonsignificant RR = 1.16 (95% CI, 0.96-1.39; $P = .11$). No drug definitely reduced mortality, overall or in any subgroup, or reduced initiation of ventilation or hospitalization duration.¹¹

META-ANALYSES OF HYDROXYCHLOROQUINE IN POST-EXPOSURE PROPHYLAXIS AND COVID-19 HOSPITALIZATIONS

The quality and usefulness of any meta-analysis depends on the quality and comparability of data from the component

trials. Combined trials should have reasonably high adherence and follow-up rates, and use comparable drugs, doses, and outcomes. The characteristics of participants and the magnitude of effects should be qualitatively similar. Such meta-analyses can be hypothesis testing if each component trial was designed a priori to test the same issue. In other circumstances such as smaller or heterogeneous trials, meta-analyses are hypothesis generating. Meta-analyses of observational studies are useful only to formulate, but not test, hypotheses. They reduce the role of chance but always introduce bias as well as uncontrolled and uncontrollable confounding because the individual trials are not randomized.¹²

Our meta-analysis of hydroxychloroquine in post-exposure prophylaxis indicates a nonsignificant RR = 0.90 (95% CI, 0.69-1.17). Thus, there is a statistically nonsignificant estimated 10% reduction in SARS-CoV-2 infection, but with sufficient precision to rule out a reduction as large as 20%.

Our meta-analysis of hydroxychloroquine in hospitalized patients with COVID-19 yields a nonsignificant RR = 1.10 (95% CI, 0.99-1.23). In hospitalized patients, there is an approximate statistically nonsignificant estimated 10% increase in mortality, but with sufficient precision to rule out a reduction as small as 1%. Further, these data suggest equality, but the point estimate is in the direction of small harm on mortality.

CONCLUSION

Previously, we recommended a moratorium to health care providers concerning prescriptions of hydroxychloroquine.^{3,13} Since that time, no significant benefits have been found in the recent randomized evidence for post-exposure prophylaxis and among hospitalized patients. Regarding risk, hydroxychloroquine derived a reassuring safety profile from decades of prescriptions for autoimmune diseases of greater prevalence in younger and middle-aged women, whose risks of fatal outcomes due to QTc prolongations are very low. In contrast, the risks associated with COVID-19 are much higher because mortality rates for COVID-19 and the side effects of hydroxychloroquine are both highest in older patients and those with comorbidities, both of whom are predominantly men. The current totality of evidence more strongly supports our previous recommendations concerning the lack of efficacy and possible harm of hydroxychloroquine in the treatment and prevention of COVID-19.

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