EDITORIAL

The Urgency of Care during the Covid-19 Pandemic — Learning as We Go

Eric J. Rubin, M.D., Ph.D., David P. Harrington, Ph.D., Joseph W. Hogan, Sc.D., Constantine Gatsonis, Ph.D., Lindsey R. Baden, M.D., and Mary Beth Hamel, M.D., M.P.H.

Chloroquine and hydroxychloroquine, alone or in combination with azithromycin, have been highly touted as potential therapies for Covid-19. The claims of efficacy are based largely on anecdotes and case series that have been described as being so persuasive that it would be unethical to perform studies with placebo controls.[1] On the basis of this "evidence," these therapies have been recommended in many guidelines, including some national policies, and have been widely implemented. But is the evidence really that strong? An observational study now published in the *Journal*[2] examines the association between hydroxychloroquine use and outcomes in patients hospitalized with Covid-19 and suggests that this treatment is not a panacea.

Geleris and colleagues studied data from 1376 consecutive patients with SARS-CoV-2 (the virus that causes Covid-19) who had been admitted to a New York City medical center between March 7 and April 8, 2020. Hospital guidance suggested the use of hydroxychloroquine for patients who had a resting oxygen saturation of less than 94% while they were breathing ambient air, but treatment decisions were at the clinicians' discretion. A total of 59% of the patients were treated with hydroxychloroquine, with 60% of those treated with hydroxychloroquine also receiving azithromycin. The authors assessed the association between hydroxychloroquine use and a composite end point of intubation or death over a median follow-up of 22.5 days.

In a simple, unadjusted comparison, the rate of death or intubation was more than twice as high among patients who received hydroxychloroquine as among those who did not. However, the clinical characteristics of the hydroxychloroquine-treated patients and of those who had not received hydroxychloroquine differed substantially. In the more detailed adjusted analyses, which were based on widely accepted methods to address confounding and selection bias, there was no evidence of a substantial difference in the rate of the composite end point of death or intubation (hazard ratio, 1.04; 95% confidence interval, 0.82 to 1.32). The findings were consistent in all the sensitivity analyses. In short, the authors used modern methods to rigorously analyze data that are available now, despite the well-understood limitations of observational studies.

For interventions that can be ethically and practically investigated in a clinical trial, evidence generated from trials with a randomized control is rightly given priority over evidence from observational studies. Even the best adjustment methods used in observational studies can miss major systematic biases, especially in the midst of a response to a pandemic with a high infection rate and associated with such rapid and high mortality. Despite this, it is difficult to ignore the accumulating and potentially valuable observational data from large medical centers and other care settings around the world. Treatment decisions are being made today without clear guidance from trial results. It is unclear when reports from high-quality controlled trials will be available.

Physicians caring for patients with Covid-19 are faced with important therapeutic choices. Should they use widely available agents such as hydroxychloroquine or azithromycin? The choice

to use these drugs has already been made, probably in hundreds of thousands of patients, but with scant evidence about the risks and benefits. We have chosen to publish this report so that clinicians will have some information that is based on rigorous analyses of available observational data. However, this observational study is in no way a substitute for randomized, placebo-controlled trials. The findings of this study set broad parameters around the potential good (or harm) that these drugs could do. The results leave open the possibility that these agents could have a modest benefit but do not rule out a detrimental effect, something that will probably be learned only through well-designed and well-conducted randomized, controlled trials. The value of such trials has been known for a century.[3] It is disappointing that several months into the pandemic, we do not yet have results from controlled trials of a therapy that is being widely used. When we have little idea about appropriate therapy, we have an obligation to help by performing studies that will help us to learn together with our patients.

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

From the Department of Biostatistics, Harvard T.H. Chan School of Public Health, and the Department of Data Sciences, Dana–Farber Cancer Institute — both in Boston (D.P.H.); and the Department of Biostatistics, Brown University School of Public Health, Providence, RI (J.W.H., C.G.).

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