Searching for COVID-19 treatments: First, do no harm

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Primum non nocere, a Latin phrase that means "first, do no harm," is attributed to the ancient Greek physician Hippocrates. It reminds healthcare professionals to consider possible harm before an intervention. The dictum of "do no harm" is the foundation of evidence-based practice in the United States. The absence of proven, specific antiviral treatments for coronavirus disease 2019 (COVID-19) has fueled the desperate need to "do something," often in the challenging setting of caring for patients with numerous life-threatening complications of infection with the causative virus. As of August 17, 2020, COVID-19 had killed over 169,000 individuals in the United States and more than 776,000 worldwide.[1,2]

Pandemics have occurred throughout history, with lasting effects on social, economic, and political aspects of civilization. The "Spanish flu" outbreak of 1918 through 1920 was the most severe pandemic in recent history, having originated from an H1N1 virus with genes of avian origin.[3,4] It killed over 500,000 Americans and approximately 50 million to 100 million people globally. The outbreak of severe acute respiratory syndrome (SARS), which affected 26 countries in 2002 and 2003 and originated from the SARS-associated coronavirus (SARS-CoV-1),[5] was the first pandemic in the 21st century. It affected fewer than 10,000 people, with a mortality rate of 10%.[6] The "swine flu" pandemic of 2009 and 2010 was caused by a descendant of the 1918-1920 H1N1 virus but had far less overwhelming repercussions. However, globally there were 60.8 million cases, 274,304 hospitalizations, and 363,550 fatalities.[7] The Ebola disease outbreak of 2014 through 2016 was indigenous to central and west Africa and led to over 28,000 cases and 11,000 fatalities.[8]

The predicament of the need to "do something" occurred in 2014 during the Ebola outbreak, when the triple monoclonal antibody cocktail ZMapp (consisting of c2G4, c4G7, and c13c6) was considered as a cure without clinical evidence.[9] Later, during a second Ebola outbreak in 2018, patients were randomly assigned to receive ZMapp, an antiviral agent (remdesivir), a single monoclonal antibody (MAb114), or, in a later-added protocol, another triple monoclonal antibody (REGN-EB3, consisting of REGN 3470, REGN 3471, and REGN 3479). The primary endpoint was death at 28 days.[10] At 28 days, death had occurred in 35.1% of patients in the MAb114 group, compared with 49.7% of those in the overall ZMapp group ($P = 0.007$); and in 33.5% of patients in the REGN-EB3 group, as compared with 51.3% of those in a subgroup of ZMapp-treated patients who were enrolled at or after addition of the REGN-EB3 group ($P = 0.002$). Overall mortality was 53.1% in the remdesivir group. The investigators concluded that both Mab114 and REGN-EB3 were superior to ZMapp in reducing deaths from Ebola disease and also showed that it was possible to conduct ethically sound clinical research in an outbreak setting.

Among possible treatments for COVID-19, the "old" drugs hydroxychloroquine (HCQ) and chloroquine were promoted because of their in vitro activity against the novel coronavirus (SARS-CoV-2) and immunomodulatory effects.[11-14] Azithromycin (AZ), a macrolide antibiotic, was also promoted because of in vitro activity against influenza A subtype H1N1 in addition to its immunomodulatory effects.[15-18] HCQ and chloroquine can cause rare and serious adverse effects, including photosensitivity, hypoglycemia, retinopathy, neuropsychiatric effects, and QT interval prolongation.[19,20] Both drugs are similar structurally to the class IA antiarrhythmic quinidine, which inhibits voltage-gated sodium and potassium channels, prolonging the QT interval and increasing the risk of torsades de pointes and sudden cardiac death.[21] The risk of proarrhythmia is greater when HCQ or chloroquine are taken concomitantly with drugs that have the potential to cause QT prolongation.[22-24] Although well tolerated, AZ has been implicated in heart rate–corrected QT interval (QTc) prolongation, proarrhythmic events, and dose-dependent elevation in QTc values when combined with chloroquine.[15] Primary outcomes of cardiovascular and sudden death were evaluated in a retrospective cohort study among 7,824,681 antibiotic exposures (22% to AZ and 78% to amoxicillin) in the outpatient setting. AZ use was associated with significantly increased hazards of cardiovascular death (hazard ratio [HR], 1.82; 95% confidence interval [CI], 1.23-2.67) and all-cause mortality (HR, 2.00; 95% CI, 1.51-2.63) within 5 days of exposure.[25] An analysis of the World Health Organization pharmacovigilance database compared cardiovascular adverse drug reactions (ADRs) among patients who received HCQ or AZ alone or in combination against cardiovascular ADRs associated with all other drugs.[26] The cases were retrieved from a total of 21,275,867 ADR reports in the database.

There were 76,822 cardiovascular ADR reports associated with use of HCQ alone, 89,692 reports associated with use of AZ alone, and 607 reports associated with combination therapy. HCQ was associated with heart failure and suspected to be the offending agent in 28% of the cases, and AZ was implicated in 61% of the cases. AZ was associated with more incidents of prolonged QT and ventricular tachycardia than HCQ, whereas the drug combination was associated with greater numbers of both ADRs than either drug individually. The time to onset of a cardiovascular ADR was 3 days with AZ use and 51 days with HCQ use. One large study evaluated claims data from 14 sources and electronic medical records from Germany, the United Kingdom, Japan, Netherlands, Spain, and the United States to assess severe adverse events (SAEs) in new users of HCQ and in individuals who received HCQ with subsequent addition of AZ (this study was not peer reviewed).[27] A total of 956,374 new HCQ users and a total of 323,122 users of HCQ and AZ combination therapy were identified. No excessive risk of SAEs was associated with short-term HCQ treatment. However, significant risks were identified for users of HCQ plus AZ. There was an observed 15% to 20% increased risk of angina or chest pain and heart failure, as well as a 2-fold risk of cardiovascular mortality in the first month of treatment. In addition, indiscriminate use of AZ, a commonly used antibiotic, may cause increased antimicrobial resistance, an unintended consequence of inappropriate use.

An early anecdotal, observational, nonrandomized, open-label, nonblinded study of 42 patients in France found improved virological clearance with use of HCQ and AZ combination therapy.[28] Twenty-six confirmed SARS-CoV-2–positive patients who received HCQ, 6 of whom received concomitant AZ therapy, were compared to a control group of 16 untreated patients at another facility. The researchers compared viral titers in the 2 groups. Within 6 days, virological clearance was observed in 70% of the HCQ recipients and 12% of controls ($P < 0.001$). Among all 20 patients who received HCQ, 6 of 6 (100%) who also received AZ had viral clearance, compared to 8 of 14 (57%) who received HCQ monotherapy. However, data on viral load (assessed via polymerase chain reaction [PCR] assay) was missing for at least 4 of 7 possible assay days among patients in the control group, compared to no more than 2 days of missing values in the treatment group. Patients in the HCQ and AZ group had lower viral loads compared to the controls at the time of treatment initiation, with the likely possibility that they were at a later stage of infection. Six patients in the HCQ arm (who tended to be more ill than patients in the other study arms) were lost to follow-up due to early cessation of treatment (3 required transfer to an intensive care unit [ICU], 1 died, 1 left the hospital, and 1 experienced nausea and stopped treatment) and were excluded from the analysis, raising serious questions about the scientific validity of the study results. The study's design had major methodological flaws, including small sample size; unvalidated surrogate endpoints; lack of randomization and blinding; and lack of mortality, complication, and safety data. The professional society that publishes the journal in which the findings were reported (ie, the International Society of Antimicrobial Chemotherapy) later released a statement noting that the article did not meet its standards.[29]

Despite the study's severe methodological flaws, the findings were disseminated rapidly by the lay press and social media and endorsed by institutional leaders, with subsequent massive adoption by clinicians worldwide. Prescriptions for HCQ and chloroquine (less than 28 tablets) surged nearly 2,000% compared with the same week in the previous year.[30] In total, there were roughly 500,000 excess fills of prescriptions for HCQ and/or chloroquine in the United States from February 16 through April 25, 2020, compared with a similar period in 2019.

Lack of clinically relevant endpoint evidence did not deter the Food and Drug Administration (FDA) from issuing an emergency use authorization (EUA) on March 28, 2020. This allowed the distribution of HCQ and chloroquine from the Strategic National Stockpile to treat hospitalized patients with COVID-19 for whom a clinical trial was not available.[31] The authorization resulted in confusion by giving the impression that FDA had approved the drugs for COVID-19 treatment. This prompted many health systems to include HCQ in their treatment protocols. Soon, 31 million doses of HCQ and chloroquine were donated by pharmaceutical companies to the Strategic National Stockpile and distributed among the nation's health systems for widespread use.[32] A similar situation occurred during the 2009-2010 swine flu outbreak when FDA authorized an EUA to allow the use of peramivir, an investigational agent, in 1,200 to 1,500 severely ill hospitalized patients with H1N1 influenza. Later, a randomized clinical trial failed to show any benefit of peramivir use in severely ill hospitalized patients.[33] Based on the trial data, peramivir was approved for the treatment of uncomplicated influenza—but not for hospitalized critically ill patients—in 2014.

The authors of the aforementioned French study[28] reported a case series of 80 hospitalized patients (included 6 patients from their previous study) who received both HCQ and AZ.[34] In that case series, 83% of patients had negative nasopharyngeal PCR assay results on day 8, and viral cultures for selected patients were negative on day 5 in 97.5% of those tested; 92% of patients were considered to be at low risk for clinical deterioration based on age, respiratory rate, oxygen saturation, temperature, blood pressure, pulse, and level of consciousness. Only 15% had fever, and 4 patients were asymptomatic carriers. Only 12% required oxygen therapy, which argues against the need for hospitalization. The available documented PCR results began to diminish on day 3, and by day 6 only 60 of the original 80 patients were represented by the data. Like the previous report, it had major design and reporting flaws, including flaws related to patient selection, PCR studies, cultures and lack of a control group. Similarly, other reports on clinical outcomes of

HCQ or chloroquine use in patients with COVID-19 are not encouraging in that the studies also had serious methodological flaws, including small sample size, open-label design, and a lack of clinical endpoints and controls.[35-38]

An observational, propensity score–matched cohort study involving 807 patients funded by the National Institutes of Health (NIH) found no evidence that the use of HCQ, either with or without AZ, reduced the need for mechanical ventilation in hospitalized patients with COVID-19.[39] The risk of death from any cause was significantly higher in the HCQ group vs the no-HCQ arm (HR, 1.83; 95% CI, 1.16-2.89; P = 0.009) but not in the group treated with HCQ plus AZ (HR, 1.31; 95% CI, 0.80-2.15; P = 0.28) as compared to the no-HCQ arm. The risk of a need for mechanical ventilation was not significantly different in the HCQ group (HR, 1.19; 95% CI, 0.78-1.82; P = 0.42) or the group treated with HCQ plus AZ (HR, 1.09; 95% CI, 0.72-1.66; P = 0.69) in comparison to the no-HCQ group. Another observational, propensity score–matched cohort study involving 181 patients at 4 hospitals in France found no significant differences in the primary outcome of survival without transfer to the ICU at day 21 between those who took HCQ and those who received standard supportive care (76% with HCQ use vs 75% in controls; HR, 0.9 [95% CI, 0.4-2.1]).[40] The overall survival rate at day 21 was 89% in the HCQ arm compared to 91% in the control arm (HR, 1.2; 95% CI, 0.4-3.3). In an open-label multicenter trial at 16 hospitals in China, 150 patients were randomly assigned (1:1) to receive HCQ plus standard of care or just standard of care. The rate of occurrence of the primary endpoint of negative SARS-CoV-2 conversion by day 28 was 85.4% in the HCQ arm and 81.3% in the standard of care arm.[41] The median time to negative conversion was also similar in the HCQ arm compared to the standard of care group (HR, 0.85; 95% CI, 0.58-1.24; P = 0.34). Thirty percent of the patients treated with HCQ had adverse events, compared to 8.8% in the control group (P = 0.001). The primary outcome of in-hospital mortality was evaluated in an retrospective, multicenter, observational cohort study of 1,438 patients at 25 New York hospitals.[42] There were no significant differences in mortality between patients who received only standard care but no pharmacotherapy and those who received HCQ alone (HR, 1.08; 95% CI, 0.63-1.85), HCQ plus AZ (HR, 1.35; 95% CI, 0.76-2.13), or AZ alone (HR, 0.56; 95% CI, 0.26-1.21). In an observational, propensity–matched cohort study of 1,376 consecutive patients with COVID-19 who were treated at a New York City hospital, those who received HCQ with or without AZ were matched with those who did not receive HCQ.[43] The primary endpoint of risk of intubation or death was not significantly higher or lower in either of the 2 patient groups (HR, 1.04; 95% CI, 0.82-1.32). The investigators concluded that they could not support the use of HCQ until randomized clinical trials supported its use. A large randomized controlled trial involving over 11,000 patients in the United Kingdom assessed the efficacy of HCQ and 5 other treatments for prevention of death compared with usual care alone (this study also was not peer reviewed).[44,45] In that study, 1,542 patients were randomly assigned to receive HCQ along with usual care and compared to 3,132 patients who received usual care alone. The primary endpoint of 28-day mortality occurred in 25.7% of patients in the HCQ arm and 23.5% of those in the usual care arm (HR, 1.11; 95% CI, 0.98-1.26; P = 0.10). In addition, there was no evidence of benefits in terms of the duration of hospitalization or other outcomes. In a randomized allocation-concealed, placebo-controlled, double-blind trial, 821 asymptomatic patients exposed to known COVID-19 cases were evaluated for postexposure prophylaxis with HCQ.[46] The patients' average age was 40 years and 70% did not have any comorbidities. Overall, 87.6% of the participants reported a high-risk exposure to a confirmed COVID-19 contact. Four hundred fourteen patients who received HCQ for 5 days were compared to 407 patients who received a placebo. The primary outcome of new symptomatic illness was observed in 11.8% of patients in the HCQ vs 14.3% of those in the placebo arm during 14 days of follow-up (P = 0.35).

Evidence of potential harm from use of HCQ and/or chloroquine became apparent, as well. For example, a randomized double-blind trial involving 81 patients in Brazil compared high-dose chloroquine (600 mg twice daily for 10 days) vs low-dose chloroquine (450 mg twice daily for 1 day, followed by 450 mg daily for 4 days and then placebo use for 5 days).[47] All patients were treated with ceftriaxone for 7 days and AZ for 5 days; 89.6% of patients also received oseltamivir. The mortality rate by day 13 was 39% in the high-dose group and 15% (P = 0.03) in the low-dose group (HR, 3.6; 95% CI, 1.2-10.6); 18.9% of patients who received the high dosage had a QTc interval of >500 milleseconds (ms), compared to 11.1% of those in the low-dosage arm. The trial investigators originally planned to enroll 440 patients, but the study was halted by the data safety and monitoring board due to concerns regarding safety and lack of clear benefit. In a retrospective study in the United States, 84 patients with COVID-19 treated with both HCQ and AZ were assessed for effects on QTc interval[48]; 11% of the patients developed a QTc interval of >500 ms, and QTc increased by 40 ms in 30% of patients.

An observational case series assessed QTc effects of HCQ with or without AZ in 40 patients.[49] In patients treated with HCQ and AZ, 6 of 18 (33%) developed an increase in QTc of 500 ms or greater, compared with 1 of 22 (5%) of those treated with HCQ alone (P = 0.03). A cohort study of 90 hospitalized patients evaluated risk of QTc prolongation with use of HCQ alone or in combination with AZ. Nineteen percent of patients receiving HCQ alone developed a QTc interval of ≥500 ms, compared to 21% of those on the combination regimen.[50] One patient developed torsades de pointes 3 days after discontinuation of HCQ and AZ. The patient had severe bradycardia, acute respiratory distress syndrome, hypothermia, and a new cardiomyopathy, raising concerns that the

risk of QTc prolongation likely persisted because of the prolonged terminal half-life of both HCQ and AZ. The American Heart Association, American College of Cardiology, and Heart Rhythm Society have recommended to withhold use of HCQ and AZ in patients with baseline QT prolongation or with known congenital QT syndrome.[51] Unintentional poisoning is another consequence of uninformed use of these agents. Chloroquine phosphate is used to treat water in home aquariums. The pandemic has fueled the purchase of this product to self-medicate for COVID-19 and resulted in numerous unintentional poisonings and at least 1 fatality.[52] Based on the growing number of cardiac adverse events in patients with COVID-19, FDA cautioned against HCQ or chloroquine use outside of a hospital or in a clinical trial because of a risk of heart rhythm problems on April 24, 2020.[53]

Finally, FDA revoked the EUA for HCQ and chloroquine on June 15, 2020.[54] The agency stated that "in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweigh the known and potential risks for the authorized use." Shortly thereafter, both NIH and the World Health Organization decided to halt ongoing clinical trials of HCQ after determining use of the drug in COVID-19 had no benefits.[55,56] From a policy perspective, the EUA was a complete failure. The premature decision by FDA facilitated uncontrolled use of HCQ rather than determination of effectiveness and safety via randomized clinical trials. Adverse events secondary to indiscriminate use of HCQ could have been avoided as well. Given that the agency is so steeped in protocol and process, it is puzzling how FDA arrived at its decision to allow the EUA in the first place. In contrast, remdesivir, an antiviral agent, received an EUA from FDA on May 1, 2020, after a placebo-controlled, randomized trial demonstrated a shorter time to recovery with use of the drug.[57]

The COVID-19 pandemic has placed intense pressure on clinicians to use unproven therapies. Hype around unproven treatments is misguided, but the hope is understandable. However, abandoning the principles of evidence-based practice is dangerous. At a time of grave distress, evidence is the key to finding an effective treatment and to avoiding misinformation coming from unscientific resources, such as the media. These developments are real dangers to the US drug approval process, which requires evidence of efficacy and safety based on well-controlled trials. Recently, the president of the American Medical Association called for all leaders to affirm science, evidence, and facts in their words and actions.[58] After reviewing all of the available evidence, the Infectious Diseases Society of America issued guidelines for managing COVID-19 that recommended against use of hydroxychloroquine, with or without azithromycin, or any other commercially available drug outside of a clinical trial. Other expert guidelines have recommended the same.[59-63]

FDA has transformed radically from the days of approving drugs without any proven efficacy or safety to the current 3 phases of clinical studies to test dosage, efficacy, safety, and adverse effects.[64,65] The agency has evolved into the world's foremost authority on conducting and evaluating controlled clinical trials for the overwhelming majority of drugs that are approved in the United States prior to approval in Canada or Europe.[66] There are several hundred clinical trials focused on COVID-19 underway around the globe, and thus the knowledge on treatment of COVID-19 will continue to evolve.[67] Once the data become available, FDA then has the ability to approve an effective and safe drug within a short time.

FDA is the gatekeeper to protect the public health and is critical to sustain US global leadership in drug innovation. Our foundation of evidence-based clinical practice is based on large, well-designed randomized controlled trials. The failure of HCQ against COVID-19 stands as prime example of the urgent need for adherence to science. Rigorous scientific objectivity and independence must prevail in any future EUA decision by FDA. Trust in FDA's mission to approve safe and effective medications was built over decades by the capable scientists working for the agency, and the integrity of public trust must be protected to conquer future pandemics and ensure safe use of vaccines against COVID-19 once they become available.

Disclosures

The authors have declared no potential conflicts of interest.

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