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Opinion: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis

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Running Head: Outpatient Treatment of High-Risk Covid-19

Abstract

More than 1.6 million Americans have been infected with SARS-CoV-2 and >10 times that number carry antibodies to it. High-risk patients presenting with progressing symptomatic disease have only hospitalization treatment with its high mortality. An outpatient treatment that prevents hospitalization is desperately needed. Two candidate medications have been widely discussed: remdesivir, and hydroxychloroquine+azithromycin. Remdesivir has shown mild effectiveness in hospitalized inpatients, but no trials have been registered in outpatients. Hydroxychloroquine+azithromycin has been widely misrepresented in both clinical reports and public media, and outpatient trials results are not expected until September. Early outpatient illness is very different than later hospitalized florid disease and the treatments differ. Evidence about use of hydroxychloroquine alone, or of hydroxychloroquine+azithromycin in inpatients, is irrelevant concerning efficacy of the pair in early high-risk outpatient disease. Five studies,

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including two controlled clinical trials, have demonstrated significant major outpatient treatment efficacy. Hydroxychloroquine+azithromycin has been used as standard-of-care in more than 300,000 older adults with multicomorbidities, with estimated proportion diagnosed with cardiac arrhythmias attributable to the medications 47/100,000 users, of which estimated mortality is <20%, 9/100,000 users, compared to the 10,000 Americans now dying each week. These medications need to be widely available and promoted immediately for physicians to prescribe.

Keywords: Azithromycin; Covid-19; Doxycycline; Hydroxychloroquine; Remdesivir; SARS-CoV-2; Zinc

Abbreviations: AZ, azithromycin; CDC, US Centers for Disease Control; FAERS, FDA Adverse Events Reporting System database; FDA, US Food and Drug Administration; HCQ, hydroxychloroquine; NIH, US National Institutes of Health; QTc, corrected electrocardiogram Q-T-wave duration; RCT, randomized controlled trial; RR, relative risk; R_t, epidemic reproduction number at time *t*.

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Introduction

Aside from the now more than 1.6 million Americans found through testing and public-health reporting to be infected with SARS-CoV-2, seropositivity studies in California (1, 2), Colorado (3) and New York City and State (4) suggest that some 10-50-fold larger numbers of people carry antibodies to the virus. The workforce and effort required to carry out contact-tracing on these tens of millions of Americans is not practical. While these studies have generated some media criticism, recent similar studies of blood donor samples in the Netherlands found 3% with SARS-CoV-2 antibodies (5), and 5% among household volunteers in Spain (6). Even allowing for some degree of false-positivity of these antibody tests, they still indicate that appreciably larger fractions of the population have been infected than have been characterized by identified reported cases. "Flattening the curve," by social distancing, mask wearing and staying at home, serves to reduce hospital loads and spread them out over time, but to-date has pushed infection reproduction numbers R_t down only to about 1.0 (7), thus even if maintained, over time very large numbers of people in the US may eventually get the infection. The great majority of infected people are at low risk for progression or will manifest the infection asymptomatically. For the rest, outpatient treatment is required that prevents disease progression and hospitalization. Exposures will occur as isolation policies are lifted and people begin to mix, even with various degrees of public isolation such as mask usage and physical separation still in place. Thus, *the key to returning society toward normal functioning and to preventing huge loss of life*, especially among older individuals, people with comorbidities, African Americans and Hispanics and Latinos, *is a safe, effective and proactive outpatient treatment that prevents hospitalization in the first place*.

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All treatments have costs and benefits. In an ideal world, randomized double-blinded controlled clinical trials establish evidence for the relative degree of benefit, and if large enough, for estimates of the frequencies of adverse events. These trials take time to conduct: to get formal approval, to get funding, to enroll enough eligible patients, to wait for the outcomes to occur, and to analyze the data. In the context of the Covid-19 pandemic, we are presently averaging about 10,000 deaths per week in the US, under moderately strong isolation policies that have put more than 36 million people out of work. Results of currently ongoing or planned randomized trials for use of a number of outpatient medications are many weeks or months off, and there are no guarantees that the results for these agents, even if statistically significant, will show sufficient magnitudes of effectiveness to be useful clinically. We are rapidly reaching a breaking point in the ability to maintain the status quo; states have begun the process of lifting their restrictions, and we thus need to evaluate what evidence we do have for promising outpatient treatments.

Review of Evidence

Based on laboratory and other preliminary evidence to-date, among many others, two candidate medication regimens have been widely discussed for outpatient treatment: remdesivir (Gilead Sciences, Inc., Foster City, California), and hydroxychloroquine (HCQ) plus azithromycin (AZ). Remdesivir has been studied extensively in laboratory work and in animals (8) and for other viral diseases and has good biological properties, suggesting utility for SARS-CoV-2 infection. In a study of remdesivir compassionate use in 53 hospitalized patients with severe disease (9), 13% died, which appears lower than what might have been expected without treatment, though greater than the deaths in the placebo arm of the Adaptive COVID-19

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Treatment Trial (more below). In a randomized, controlled but relatively underpowered trial in severe non-ventilated hospitalized patients in China (10), benefit vs placebo was not able to be shown either in improvement or mortality. An appreciable fraction of the remdesivir patients left the trial early because of serious adverse events. The Adaptive COVID-19 Treatment Trial of hospitalized patients with advanced lung disease has released initial results (11) showing that patients on remdesivir had 31% faster recovery than patients on placebo, medians 11 vs 15 days, which difference was statistically significant, but these results involve patients who did indeed survive. Mortality of the two groups, 8.0% vs 11.6%, respectively, was better for remdesivir but not significantly so (*P*-value=.059). More specific for consideration here, remdesivir has not been studied in outpatient use. The Scientists to Stop Covid-19 "secret" Report (12, p. 7) recommends widespread use of remdesivir, and "as early in infection as possible," but no actual evidence as yet shows in humans that it would be helpful for routine outpatient circumstances and disease. The FDA recently approved use of remdesivir in the current public-health emergency circumstances (13), but only for patients with "severe disease defined as SpO2≤94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)" and "administered in an in-patient hospital setting via intravenous (IV) infusion by a healthcare provider." This approval seems specifically not to allow outpatient use. Symptomatic outpatient infection is a pathologically and clinically different disease than the life-threatening inpatient acute respiratory distress syndrome caused by SARS-CoV-2, thus there is little reason to think that the same treatment would be useful for both (14). In any event, none of 20 currently registered trials is scheduled to provide data on outpatient use of remdesivir, thus we may not know whether it could be used effectively to prevent hospitalization of symptomatic outpatients unless or until it is actually tried that way.

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The other suggestion is the combined regimen of HCQ+AZ (or its variant HCQ+doxycycline). The FDA has recently issued guidance (15) to physicians and the general public advising that the combination HCQ+AZ should not generally be used except by critically ill hospital inpatients or in the context of registered clinical trials. The NIH panel for Covid-19 treatment guidelines say essentially the same (16), and a similar statement has been released by the major cardiology societies (17). Numerous reviews of HCQ efficacy and adverse events have been and continue to be published. To my knowledge, *all of these reviews have omitted the two critical aspects of reasoning about these drugs: use of HCQ combined with AZ or with doxycycline, and use in the outpatient setting*. For example, the Veterans' Administration Medical Centers study (18) examined treated *hospitalized* patients and was fatally flawed (19). The same point about outpatient use of the combined medications has been raised by a panel of distinguished French physicians (20) in petitioning their national government to allow outpatient use of HCQ+AZ. It appears that the FDA, NIH and cardiology society positions have been based upon theoretical calculations about potential adverse events and from measured physiologic changes rather than from current real-world mortality experience with these medications and that their positions should be revised. In reviewing all available evidence, I will show that HCQ+AZ and HCQ+doxycycline are generally safe for short-term use in the early treatment of most symptomatic high-risk outpatients, where not contraindicated, and that they are effective in preventing hospitalization for the overwhelming majority of such patients. If these combined medications become standard-of-care, they are likely to save an enormous number of lives that would otherwise be lost to this endemic disease.

What is the evidence for these assertions? Similar to remdesivir, 16 clinical trials of HCQ+AZ are listed in the ClinicalTrials.gov database (21). Of these, only five involve treating

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outpatients with the combined HCQ+AZ regimen (Web Table 1). For the earliest trial, between now and September, assuming a flat epidemic curve of 10,000 deaths per week, I estimate that approximately 180,000 more deaths will occur in the US before the trial results are known. The CDC has estimated substantially greater numbers of deaths (22).

In this context, we cannot afford the luxury of perfect knowledge and must evaluate, now and on an ongoing basis, the evidence for benefit and risk of these medications (23). Available evidence of efficacy of HCQ+AZ has been repeatedly described in the media as "anecdotal," but most certainly is not. The evidence is not perfect either. Each piece of evidence, contained in each study, must be carefully considered and not dismissed because in an ideal world such evidence would fall in a lower part of the evidence-quality triangle. Furthermore, and most critical to the correct understanding of what evidence is available, *evidence for single agents cannot be extrapolated to apply to combined agents, evidence for one biochemical form of a drug cannot be extrapolated to another form, and even more importantly, evidence for utility or lack thereof or toxicity in hospitalized patients cannot be extrapolated to apply to outpatient use*, outpatient use comprising the sole argument for application that I am making in this review.

Thus for example, studies of chloroquine or HCQ used alone do not bear upon evidence for efficacy of HCQ+AZ or HCQ+doxycycline. This point has been argued forcefully by the French doctors (20). The first study of HCQ+AZ (24) was controlled but not randomized or blinded, and involved 42 patients in Marseilles, France. This study showed a 50-fold benefit of HCQ+AZ vs standard-of-care, with *P*-value=.0007. In the study, six patients progressed, stopped medication use and left the trial before the day-6 planned outcome measure of swab-sampled nasopharyngeal viral clearance. Reanalysis of the raw study data elsewhere (25) and by myself shows that including these six patients does not much change the 50-fold benefit. What

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does change the magnitude of benefit is presentation with asymptomatic or upper respiratory-tract infection, vs lower respiratory-tract infection, the latter cutting the efficacy in half, 25-fold vs standard-of-care. This shows that the sooner these medications are used, the better their effectiveness, as would be expected for viral early respiratory disease. The average start date of medication use in this study was day-4 of symptoms. This study has been criticized on various grounds that are not germane to the science, but the most salient criticism is the lack of randomization into the control and treatment groups. This is a valid general scientific criticism, but does not represent epidemiologic experience in this instance. If the study had shown a 2-fold or perhaps 3-fold benefit, that magnitude of result could be postulated to have occurred because of subject-group differences from lack of randomization. However, the 25-fold or 50-fold benefit found in this study is not amenable to lack of randomization as the sole reason for such a huge magnitude of benefit. Further, the study showed a significant, 7-fold benefit of taking HCQ+AZ over HCQ alone, *P*-value=.035, which cannot be explained by differential characteristics of the controls, since it compares one treatment group to the other, and the treated subjects who received AZ had more progressed pneumonia than the treated subjects receiving HCQ alone, which should otherwise have led to worse outcomes. The study has also been described as "small," but that criticism only applies to studies not finding statistical significance. Once a result has exceeded plausible chance finding, greater statistical significance does not contribute to evidence for causation (26). No different conclusion would have resulted had a study with 1000 patients found the same 50-fold benefit but with a *P*-value of 10^{-10}. Study size limitation only applies to studies having findings within the play of chance. That is not the case here.

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A second study of the Marseilles group (27) involved 1061 patients tested positive for SARS-CoV-2 and treated with HCQ+AZ for at least 3 days and followed for at least 9 days. The authors state "No cardiac toxicity was observed." Good clinical outcome and virological cure were seen in 973 patients (92%). Five patients died, and the remainder were in various stages of recovery.

The third piece of evidence involves the cohort of 1450 patients treated by Dr. Vladimir Zelenko of Monsey, NY. Dr. Zelenko has released a two-page report (28) describing his clinical reasoning and procedures, dosing conditions and regimen, and patient results through April 28. Symptomatic patients presenting to Dr. Zelenko were treated with five days of HCQ+AZ+zinc sulfate if they were considered high-risk, as evidenced by one or more of: age 60 years or older; high-risk comorbidities; body-mass index>30; mild shortness of breath at presentation. Patients were considered to have Covid-19 based on clinical grounds and started treatment as soon as possible following symptom onset, rather than delaying for test results before starting treatment. Of the 1450 patients, 1045 were classified as low-risk and sent home to recuperate without active medications. No deaths or hospitalizations occurred among them. Of the remaining 405 treated with the combined regimen, 6 were ultimately hospitalized and 2 died. No cardiac arrhythmias were noted in these 405 patients.

The fourth relevant study was a controlled non-randomized trial of HCQ+AZ in 636 symptomatic high-risk outpatients in São Paulo, Brazil (29). All consecutive patients were informed about the utility and safety profile of the medications and offered the treatment, and those who declined (n=224) comprised the control group. Patients were monitored daily by telemedicine. The study outcome was need for hospitalization, defined as clinically worsening condition or significant shortness of breath (blood oxygen saturation <90%). Even though the

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severities of all of the recorded flu-like signs and symptoms and of important comorbidities (diabetes, hypertension, asthma, stroke) were substantially greater in the treated patients than the controls, the need for hospitalization was significantly lower, 1.2% in patients starting treatment before day 7 of symptoms, 3.2% for patients starting treatment after day 7, and 5.4% for controls, *P*-value<.0001. No cardiac arrhythmias were reported in the 412 treated patients. The most common side effect of treatment was diarrhea (16.5%), but 12.9% of treated patients presented with diarrhea before treatment began.

Finally, a small study is ongoing in a long-term care facility in Long Island, NY. This study has been employing HCQ+doxycycline rather than HCQ+AZ for treatment of high-risk Covid-19 patients. Doxycycline itself has antiviral activity against SARS-CoV-2 at in vitro concentrations 5.6μM median (30). Among the first 54 residents treated in the Long Island study, 6 were hospitalized and 3 (5.6%) died (31). An unofficial update of these data indicates that of about 200 high-risk patients treated with HCQ+doxycycline, 9 (4.5%) have died.

The two non-randomized but controlled trials provide important evidence, if not "proof," for the major efficacy of early use of HCQ+AZ against SARS-CoV-2 infection in symptomatic high-risk outpatients. What can be said about the uncontrolled large case series of treated patients? Standard published case reports provide clinical evidence of the possibility of an exposure-outcome relationship, but not of the regularity, magnitude or representativeness of such a relationship. The same can be said of case series reports, meaning that subject entry into the series is not necessarily well-defined and no denominator information is provided from which to gauge what the series represents. However, a large series in the context of known risks of mortality or adverse events can allow for ballpark estimates of the denominator and thus provide a reasonable frame of reference for whether the outcomes likely represent beneficial or harmful

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results. For example, among Connecticut cases 60 years of age or older, at present the mortality is 20% (32). Thus, it would be ballpark to estimate that some 20% of the 1466 treated high-risk patients in the Zelenko and Marseilles cohorts would have died without outpatient HCQ+AZ treatment, 293 patients, compared to the 7 who did die. An alternative is to use the 12-13% mortality of hospitalized patients in the placebo arms of the remdesivir trials (10, 11). This would give about 180 expected deaths.

Adverse Events

Both proposed drug regimens have shown side effects. Remdesivir, in its phase-3 trial of 10-day vs 5-day therapeutic courses in hospitalized patients, produced a range of adverse events in more than 70% of patients in both treatment arms (33). Adverse events requiring medication discontinuation were many fewer, 5% in the 5-day group and 10% in the 10-day group. In the Chinese trial, 12% of remdesivir patients stopped the medication before the end of the 10-day treatment because of drug-related adverse events (10).

For HCQ+AZ use, the argued issue concerns fatal cardiac arrhythmias: the warnings issued by the FDA, the NIH and the cardiology societies. Indeed, both HCQ and AZ produce QT prolongation, rare instances of fatal Torsades de Pointes and long QT-interval syndrome. A number of essays by cardiologists published in *JAMA* and other journals have anxiously warned about these risks, but have not examined mortality from them. The sole question is whether these fatal events, or even any fatal cardiac arrhythmia events, would occur with enough frequency that general treatment of non-contraindicated high-risk outpatients by HCQ+AZ would outweigh benefit in preventing hospitalization and mortality. A number of studies have examined hospital inpatient use, but these studies have had major flaws discussed at length in the

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literature, not least of which is that patients hospitalized with multiple medical problems and more-advanced disease do not represent the mortality experience of outpatient use of these medications in patients otherwise well enough not to be hospitalized. One source of data on mortality associated with these medications is the FDA FAERS database (34). Examination of the database for adverse events reported from the beginning of the database in 1968 through 2019 and into the beginning of 2020, shows for hydroxychloroquine 1064 adverse event reports including 200 deaths for the total of cardiac causes that could be both specifically and broadly classified as rhythm-related. Of these, 57 events including 10 deaths were attributed to Torsades de Pointes and long QT-interval syndrome combined. This concerns the entirety of HCQ use over more than 50 years of data, likely millions of uses and of longer-term use than the 5 days recommended for Covid-19 treatment. For AZ use, the numbers of reported Torsades de Pointes and long QT-interval syndrome events total 37, of which 2 deaths. FAERS data are generated by patient, physician and pharmacist report initiation and likely underrepresent true event occurrences. However, even if the true numbers were 10-fold larger, they would still be minuscule compared to the amounts of medication usage. How much the risk of QT prolongation would be enhanced with HCQ and AZ taken together is unknown, but the Physicians' Desk Reference (35) says that coadministration of these medications risks “additive QT prolongation.” Not multiplicative. “Pharmacokinetic drug interactions associated with the highest risk of TdP include antifungal agents, macrolide antibiotics (except azithromycin)” (36, p. 139). Nevertheless, even if the combined HCQ+AZ produced a 10-fold higher incidence of fatal Torsades de Pointes and long QT-interval syndrome than either agent alone, and even if both events were 10-fold underreported in FAERS, thus hypothetically giving 1200 fatal events, that would still be very small compared to the millions of uses of these medications that the

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FAERS database represents. Therefore, while it is established that HCQ+AZ lengthens the QTc interval by 18-55ms on average (37-40), in 40, 84, 90 and 98 hospitalized severely ill patients in the four studies, respectively, treated with these medications and having this lengthening, a total of one case of Torsade de Pointes occurred and it was not fatal—there were no deaths. Substantial fractions of these hospitalized patients were taking diuretics, which may be contraindicated for HCQ+AZ use in the first place. This arrhythmia issue is a real, physiologically measurable effect of the use of these combined medications, but fatal arrhythmia outcomes are so rare that they are of much lesser clinical significance than the hospitalization and mortality that the drugs prevent. This fact is also clear from the lack of any cardiac arrhythmia events or arrhythmia mortality noted in the 405 Zelenko patients or the 1061 Marseilles patients or the 412 Brazil patients. Patients were not enrolled in these studies if they had known histories of QTc prolongation. History of cardiac arrhythmia or other possible contraindications for use of HCQ or AZ or doxycycline is a normal part of workup and clinical judgement in physician choice to use these medications and how to monitor the patients (see Web Appendix).

Further evidence of the real-world unimportance of arrhythmia and other cardiovascular adverse event endpoints of HCQ+AZ use is given in the large Oxford-based record-linkage study (41, 42). Fourteen large medical-records databases were examined for all-cause mortality and for 15 specified classes of adverse events among hundreds of thousands of patients with rheumatoid arthritis who had used these drugs. First, 323,122 users of HCQ+AZ were compared to 351,956 users of HCQ+amoxicillin. No significant difference in all-cause mortality was seen: as reported by the authors, relative risk (RR)=1.36, *P*-value=.10, and as I calculate from the data provided by the authors in their supplement to the paper (42), RR=1.18, *P*-value=.37; either way,

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a null association within the range of chance. However, the authors selectively presented from among the 15 analyzed endpoints the three most significant associations: cardiovascular mortality RR=2.19, *P*-value=.0088; chest pain/angina RR=1.15, *P*-value=.0027; and heart failure RR=1.22, *P*-value=.027. What is misrepresented in the authors' presentation of these data in this way is that these three outcomes were not individually specified to be of more interest than any of the other 12 specific outcomes that they examined, and they did not correct their calculated levels of statistical significance for the 15 classes of outcomes. In lay terms, a fishing expedition. When accounting is done, by the standard Bonferroni correction of multiple comparisons, the respective *P*-values are .12, .040 and .35. The large amount of data in this study thus shows that there is no significant relationship of HCQ+AZ use vs HCQ+amoxicillin use for any of the 15 outcomes specified or for all-cause mortality, except a just-barely significant association with chest pain/angina, with a 15% higher risk which even if a true finding would still be of little clinical import for a relatively infrequent outcome in the context of the mortality to be saved by HCQ+AZ use in widespread symptomatic high-risk outpatient Covid-19 treatment.

Second, the stated concern of the FDA and NIH advisories and the cardiology society opinion restricting use of HCQ+AZ was for fatal Torsades de Pointes and long QT-interval syndrome, two rare types of cardiac arrhythmias, as well as for cardiac arrhythmias in general. The Oxford study (41, 42) examined cardiac arrhythmia outcomes and obtained for its random effects meta-analysis result, RR=1.08, *P*-value=.36 for HCQ+AZ use vs HCQ+amoxicillin use. The fixed-effects meta-analysis RR=1.04, *P*-value=.41. This study clearly demonstrates that cardiac arrhythmia adverse events are not appreciably increased by combining HCQ with AZ. The same study compared HCQ use to sulfasalazine use and again found no difference in cardiac

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arrhythmia risk: for HCQ, a slightly lower RR=0.89, *P*-value=.13. The subjects analyzed in the Oxford study were largely older adults with multiple comorbidities in addition to rheumatoid arthritis.

Finally, the Oxford study allows for a direct estimate of the number of arrhythmia events attributable to HCQ+AZ use (41, 42). Among 306,106 people taking sulfasalazine (which is known not to produce QT prolongation), 877 with cardiac arrhythmias were identified, 0.287%. In 320,589 people taking HCQ+AZ, 1,068 had arrhythmias, 0.333%. The difference, 0.047% or 47/100,000 older multicomorbidity patients taking HCQ+AZ, is attributable to the HCQ+AZ use. These are events, not fatalities. As noted above, fatalities according to FAERS comprise <20% of HCQ-related arrhythmia events. The maintenance HCQ dose in the Oxford study patients, 200 mg/day, gives as large or larger plasma drug levels as five days of HCQ at 400 mg/day, the recommended dose for outpatient Covid-19. These very small numbers of arrhythmias, as well as the null results in this very large empirical study should therefore put to rest the anxieties about population excess mortality of HCQ+AZ outpatient use, either from cardiac arrhythmias, or as mortality from all causes.

This discussion thus shows that the FDA, NIH and cardiology society warnings about cardiac arrhythmia adverse events, while appropriate for theoretical and physiological considerations about use of these medications, are not borne out in mortality in real-world usage of them. Treatment-failure mortality will be much higher, but even that pales in comparison to the lives saved. It would therefore be incumbent upon all three organizations to reevaluate their positions as soon as possible. It is unclear why the FDA, NIH and cardiology societies made their recommendations about HCQ+AZ use now, when the Oxford study (41, 42) analyzed 323,122 users of HCQ+AZ compared to 351,956 users of HCQ+amoxicillin, i.e., that the

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combination of HCQ+AZ has been in widespread standard-of-care use in the US and elsewhere for decades, use comparable to HCQ+amoxicillin as if it just involved an alternate antibiotic choice, this use predominantly in older adults with multiple comorbidities, with no such strident warnings about the use given during that time. I note that since doxycycline is believed to cause even fewer cardiac arrhythmias than AZ, in patients where that is a concern (43), the long-term care-facility evidence suggests that HCQ+doxycycline likely will work about as well.

Discussion

Given that a detailed and dispassionate review of all of the available relevant evidence leads to conclusions about outpatient HCQ+AZ use different than those of the FDA and NIH panels (which comprise wider expertise than the cardiology societies), I address how different underlying scientific worldviews might be involved. This is particularly reflected in the Scientists to Stop Covid-19 position about remdesivir use "as early as possible," i.e., early outpatient use implied (12, p. 5). All but one of the scientists on the Scientists to Stop Covid-19 panel are laboratory or clinical scientists; only one is an epidemiologist. Their recommendation for remdesivir use as early as possible was made without either FDA approval or RCT evidence of efficacy in the outpatient context. This recommendation therefore appears to be an extrapolation from animal and laboratory data and from use in severely ill hospitalized patients. However, a history of epidemiology shows numerous instances of failed extrapolation from animals to humans. "Animal research on almost any topic of epidemiologic interest is so heterogeneous and inadequately synthesized that it is possible to selectively assemble a body of evidence from the animal and in-vitro studies that support almost any epidemiologic result." (44, p. 221) For example, some carcinogens have been affirmed in animal studies but not shown in

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human studies (acrylamide, alar, cyclamate, red dye #2, saccharin) (44). This is in part why the FDA has an approval system of phased RCTs leading to safety and efficacy of use in humans, *in the specific contexts* in which the drug is intended. It is not a question of off-label use, but of who are the patients for which to use the medication. For Covid-19, inpatient acute respiratory distress syndrome is typically a florid immune-system overreaction, whereas initial outpatient illness is a viral multiplication problem involving the beginnings of immune response. These are different diseases. Thus, how well remdesivir might perform in outpatients won't be known until it is tried in typical outpatient circumstances, whether in RCTs or in any other unbiased systematic study of such use. Further, to the degree that remdesivir is similar in temporal characteristics to an antiviral like Tamiflu, it would be used in general societal contexts where patients must first recognize that they might have symptoms of the disease and not something else and go to their physicians or clinics for care, and either be rapidly tested positive with an assay that has negligible false negatives, or be symptomatic enough for the disease to be clinically distinguished and diagnosed, but definably positive in this way not more than two days after symptoms start. This is a very narrow temporal window to be definitive and to obtain full antiviral effectiveness, and could be difficult to achieve in general in the mass-treatment circumstances that we are facing. So regardless of the strength of the *implied* evidence of outpatient efficacy when given shortly after the start of symptoms, remdesivir efficacy might be substantially less in the context of actual population outpatient usage. This is another reason why empirical studies of medication use in the full context of application are needed.

The extrapolation from laboratory theory to empirical use also seems to underlie resistance to the idea that combined HCQ regimens could work for early outpatient use. HCQ is known to interfere with toll-like receptor signaling, reducing dendritic cell activation and

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immune response. This would seem to be counterproductive for suppressing SARS-CoV-2 multiplication in early treatment. Again, in extrapolation from physiologic theory to human data, the epidemiologic data are definitive. The fact that epidemiologic data to-date show strong evidence for efficacy of combined HCQ+AZ in early outpatient treatment, even if not "proof" yet at the level of several successful RCTs, is evidence that this medication regimen works in that context. The clash in scientific worldviews is that basic and clinical scientists seem to feel that biological and drug-development evidence for medication use in non-human and non-outpatient contexts can be extrapolated to recommendations for outpatient use without benefit of RCT evidence but don't accept epidemiologic evidence without RCTs, whereas epidemiologists have had career experience with laboratory and animal evidence that did not hold up under epidemiologic study, but do reason by including all types of epidemiologic study designs and derive causal conclusions in the standard way following Hill's Aspects (26) on the basis of strong totality of evidence, sometimes even without RCT evidence. There are contexts where each approach is valid. However, it is not my point to say that remdesivir has little evidence to support its potential outpatient utility, only efficacy considerations that have not been addressed and that could lead to lack of efficacy under general use, but that HCQ+AZ has been directly studied in actual early high-risk outpatient use with all of its temporal considerations and found empirically to have sufficient epidemiologic evidence for its effective and safe employment that way, and that requiring delay of such general use until availability of additional RCT evidence is untenable because of the ongoing and projected continuing mortality. No studies of Covid-19 outpatient HCQ+AZ use have shown higher mortality with such use than without, cardiac arrhythmias included, thus there is no empirical downside to this combined medication use.

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Some of my medical colleagues still prefer to wait until more studies are done and stronger evidence such as from RCTs becomes available, and government and professional advisory panels do reevaluate the evidence. I strongly urge these panels to reconsider the data and arguments discussed above. Substantial fractions of physicians treating Covid-19 patients in Europe and elsewhere report use of HCQ+AZ: 72% in Spain, 49% in Italy, 41% in Brazil, 39% in Mexico, 28% in France, 23% in the US, 17% in Germany, 16% in Canada, 13% in the UK (45), much of the non-US use in outpatients. HCQ+AZ has been standard-of-care treatment at the four New York University hospitals, where a recent study showed that adding zinc sulfate to this regimen significantly cut both intubation and mortality risks by almost half (46). The French physicians are insistent that with careful clinical judgement and supervision, these medications are safe and should be used as early as possible for outpatients, and they provide a detailed clinical guide to their use (20). Until we have quantitative evidence for the utility and safety of other medications for preventing hospitalization and mortality in high-risk Covid-19 outpatients, the urgency of current mass mortality requires an immediate application of the best that we have available, even if knowledge is imperfect and even if yet unproven to the standards of double-blinded RCTs. This problem will get even worse as states and cities yield to the acute pressure at this moment to begin lifting stay-at-home restrictions and even more people become infected. Some people will have contraindications and will need other agents for treatment or to remain in isolation. But for the great majority, I conclude that HCQ+AZ and HCQ+doxycycline, preferably with zinc (47) can be this outpatient treatment, at least until we find or add something better, whether that could be remdesivir or something else. It is our obligation not to stand by, just "carefully watching," as the old and infirm and inner city of us are killed by this disease and our economy is destroyed by it and we have nothing to offer except high-mortality hospital

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treatment. We have a solution, imperfect, to attempt to deal with the disease. We have to let physicians employing good clinical judgement use it and informed patients choose it. There is a small chance that it may not work. But the urgency demands that we at least start to take that risk and evaluate what happens, and if our situation does not improve we can stop it, but we will know that we did everything that we could instead of sitting by and letting hundreds of thousands die because we did not have the courage to act according to our rational calculations.

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