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COMMENTARY

Flattening the Risk: Pre-Exposure Prophylaxis for COVID-19

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Abstract: To date, more than 35 million people worldwide have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent of coronavirus disease 2019 (COVID-19), and more than one million have died in the COVID-19 pandemic. International economies are stalled and social isolation based on palpable fear of death remains the order of the day. The United States and other countries are moving toward resuming work activities and social interaction to boost economic recovery. While this makes financial sense, from a medical perspective our population has already suffered and will continue to suffer severe losses in the absence of a viable aggressive prophylaxis strategy for SARS-CoV-2. Herein, we present a plan to address this problem.

Keywords: coronavirus, SARS, COVID-19, prophylaxis

Introduction

The medical approach to SARS-CoV-2 is based on three principles: prevention, early treatment and late treatment. We previously presented a novel plan to implement early treatment for COVID-19 on a large scale as needed.[1] Although this plan may salvage patients with early disease, it is less practical than prevention for people who are resuming work activities and who may be exposed to SARS-CoV-2 via contact, aerosol and/or droplet transmission.[2] As for late treatment, the high mortality rate of 50% or more for patients on respiratory support makes implementation of prevention and early treatment an urgent priority.[3] Furthermore, the emergence of persistent debilitating symptoms in survivors indicates that COVID-19 is a complex illness that is best avoided.[4] Residual risk of COVID-19 will likely persist in the future, and this risk is associated with additional global mental health problems such as stress, anxiety, depressive symptoms, insomnia, denial, anger and fear.[5,6] The medical costs of a poorly controlled COVID-19 pandemic are projected to reach hundreds of billions of dollars in the United States.[7]

Prophylaxis for viral infections traditionally relies on vaccines. Although a vaccine for COVID-19 would be an optimal solution, the prospects for a safe and effective vaccine are murky at best and probably not a viable option in the next two years due to mutational variation of the virus and potential vaccine enhancement of viral infection.[8,9] Herd immunity to SARS-CoV-2 also may be difficult to achieve because the infection rate is too low.[10,11] Therefore, an alternate prevention strategy is needed when social distancing is phased out during economic recovery. Drawing on lessons from the HIV/AIDS pandemic, we know that pre-exposure prophylaxis (PrEP) with antiviral agents is a viable strategy to prevent infection.[12] In the case of

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HIV/AIDS, however, this treatment-intensive and expensive strategy only works because of the relatively small number of subjects at risk. For the COVID-19 pandemic, we need a more practical approach to prevention.

Based on worldwide experience with SARS-CoV-2, we now know that certain groups carry a higher risk of developing severe complications of COVID-19.[3,13,14] These groups can be classified according to the following risk factors:

- Hypertension
- Diabetes
- Obesity
- Chronic kidney disease
- Asthma/emphysema/smoking
- Congestive heart failure
- Liver cirrhosis
- Malignancy/immune suppression
- Age over 80 years old

In addition, medical personnel have more than three times the risk of acquiring the disease from repeated exposure to infected patients and household contacts.[15,16] As schools reopen and asymptomatic children increase the risk of viral transmission, more teachers and parents will need protection against viral infection.[17] Other high-risk groups include first responders, factory workers and sailors confined to close quarters, and prisoners.[18] Individuals with certain genotypes may also have increased susceptibility to severe COVID-19.[19] These subjects would benefit from a simple PrEP-type treatment for SARS-CoV-2.

Hydroxychloroquine PrEP

Where can we find a prophylactic treatment that is easy to use, inexpensive and already available? One answer lies in a medication that has generated significant controversy so far in the pandemic: hydroxychloroquine (HCQ). This medication has been used in combination with azithromycin for treatment of established SARS-CoV-2 infection, with variable results.[20,21] There has been concern about cardiac and retinal toxicity with high-dose HCQ, especially because azithromycin increases blood levels of the medication.[22,23] Furthermore, shortages of the two antimicrobials have occurred due to overprescribing in the face of the pandemic. Nevertheless, the combination appears to be effective in patients with early COVID-19, although it appears to be less effective in hospitalized patients with advanced disease.[20,21] HCQ treatment was shown to protect multiple organs from inflammation in hospitalized COVID-19 patients.[24] In one uncontrolled study, HCQ prophylaxis in a hospital setting with a known SARS-CoV-2 exposure prevented dissemination of viral infection.[25]

An overlooked property of HCQ is its extremely long half-life, estimated at up to 40 days with oral dosing.[26,27] This extraordinary property has allowed the medication to be used for decades as weekly prophylaxis for malaria.[28,29] Although HCQ-resistant malaria has eventually developed in parts of the world, the benefit of the medication is still recognized in terms of low cost, ease of use and limited side effects in areas with susceptible disease.[29–31] Malaria prophylaxis with HCQ may contribute in part to the reportedly low rate of COVID-19 infection seen so far in sub-Saharan Africa.[32,33] Data from three randomized clinical trials using HCQ for the prevention and treatment of COVID-19 did not suggest significant safety concerns, and there were no sudden deaths in any trial.[34] HCQ treatment is also considered safe for use in pregnancy and childhood diseases.[35,36] Unfortunately, extrapolation of inpatient HCQ use to outpatient settings has muddied both the risks and benefits of this readily available preventive treatment for COVID-19.[37]

Based on these observations, we propose instituting a prophylactic regimen for SARS-CoV-2 in the high-risk patients listed above. The dose limit should be 400mg weekly based on malaria prophylaxis recommendations and continuing for one month or longer depending on the degree of social interaction and risk of viral exposure. The use of this prophylactic regimen will allow individuals to resume work with some modicum of protection against COVID-19. PrEP would also prevent high-risk individuals from acquiring infection from close contacts infected with the virus, and it would hopefully attenuate SARS-CoV-2 infection if it did occur.[13] Although a higher-dose regimen might be more effective, higher dosing would also increase the risk of adverse events without clear benefit at this point in the pandemic.[38,39] If symptoms of COVID-19 develop despite the use of PrEP, further treatment should be instituted immediately, as outlined in our previous publication.[1]

Recently three studies of HCQ prophylaxis in healthcare workers (HCWs) from India reported encouraging results. One cohort study found that 38% of untreated HCWs developed COVID-19 infection compared to 7% of HCWs treated with weekly HCQ PrEP ($p<0.001$).[40] The second case–control study of HCWs found that four or

more weekly doses of HCQ resulted in significantly less infection with SARS-CoV-2 (adjusted odds ratio 0.44, p<0.001).[41] The third study was a questionnaire-based analysis showing that HCWs who had taken a full course of HCQ PrEP (seven or more weekly doses) had significantly less infection with SARS-CoV-2 compared to those who had taken either an incomplete course or no HCQ at all (p = 0.021).[42]

Additional clinical observations suggest that HCQ PrEP may be effective for COVID-19. In a multicenter retrospective study of 6,228 rheumatic disease patients from China, patients who were taking HCQ had a lower risk of SARS-CoV-2 infection compared to patients taking other disease-modifying anti-rheumatic drugs (odds ratio 0.09, p=0.044).[43] Another population-based analysis of over 360,000 subjects from Portugal found that chronic HCQ treatment was associated with a significant decrease in SARS-CoV-2 infection (adjusted odds ratio 0.51, p=0.04).[44] An observational study of 1,274 early outpatient COVID-19 cases in New Jersey found that a prescription of hydroxychloroquine reduced the risk of hospitalization by 47% (odds ratio 0.53). The benefit appeared to be lost if treatment was delayed more than two days after the onset of symptoms.[45] In a retrospective cohort study of 32,109 rheumatic disease patients from the US Veterans Health Administration, the incidence of SARS-CoV-2 infection was equivalent regardless of chronic HCQ use (0.3% in users versus 0.4% in non-users), but mortality was significantly decreased in patients taking HCQ (odds ratio 0.70, p=0.0031).[46] HCQ PrEP failed to prevent experimental viral infection in Syrian hamsters and macaque monkeys, but all of the animals cleared their infections and none died. Thus, the hamster and monkey PrEP models have questionable significance for humans.[47,48]

Larger randomized controlled trials (RCTs) of HCQ PrEP are ongoing in the United States and elsewhere.[49–52] The results of two RCTs that enrolled 1,615 HCWs were recently released, and among 1,053 subjects who received HCQ PrEP there were no hospitalizations, no deaths and no cardiac complications. In addition, once-weekly dosing appeared to be as effective as twice-weekly or daily dosing for HCQ PrEP. Because the studies were terminated prematurely they were underpowered to show a treatment benefit, however.[53,54] Since RCTs require an average of 5.5 years for completion at an average cost of over a million dollars, it may take a long time to obtain conclusive results from these studies.[55–57] In the face of a public health crisis, it is important to consider life-saving approaches based on scientific logic and clinical availability even if definitive results are pending.[21,58]

Mefloquine PrEP

Unfortunately, HCQ has generated significant controversy resulting in the public perception that the medication is dangerous and ineffective. In light of this problem, weekly prophylaxis with mefloquine 250mg could be used instead. This oral medication has a half-life of about three weeks and appears to be active against SARS-CoV-2 in vitro, which makes it suitable for weekly antiviral prophylaxis.[59,60] The troubling neuropsychiatric side effects of mefloquine make the drug a less attractive option for PrEP.

Ivermectin PrEP

Another option is the antiparasitic drug ivermectin. This antimicrobial agent with antiviral properties appears to be effective against SARS-CoV-2 in vitro and in vivo.[61–64] The half-life of ivermectin is 12–36 hours in humans, and its metabolites may persist for up to 12 days due to high liposolubility. It can be dosed daily or weekly at 0.15–0.2mg/kg with minimal side effects, but clinical PrEP trials for COVID-19 using ivermectin have not been organized to date, and appropriate antiviral dosing remains questionable.[65] Individuals with specific gene mutations may have adverse reactions to ivermectin.[66]

Tafenoquine PrEP

Tafenoquine, a newer antimalarial agent that can be dosed weekly with a half-life of 2–3 weeks, has been suggested for COVID-19 PrEP, but the side effects and cost of this medication make it a less attractive candidate for widespread prophylaxis.[67,68]

Other Medication Options for PrEP

In patients with HIV/AIDS, treatment with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) lowered the risk of COVID-19, but these medications are expensive and must be dosed daily.[69] Therapy with convalescent plasma has been administered to severely ill COVID-19 patients and prophylaxis with plasma or neutralizing monoclonal antibodies has been suggested, but use of these nascent non-standardized treatments for PrEP has not been evaluated.[70–74]

Barrier Protection

The efficacy and safety of barrier protection (primarily facemasks) in the COVID-19 pandemic continues to be debated, and formal studies in various settings have been recommended.[75,76] For HCWs with high-risk patient

exposure, facemasks were shown to be effective independent of other preventive measures.[42] For the general population, facemasks appear to be less effective due to technical limitations, compliance issues and variable transmission risks.[75,76] The theory of "variolation", which states that population-wide masking may limit viral load exposure and thereby attenuate the severity of COVID-19, remains to be proven.[77] Although not a perfect solution, medication-based PrEP should largely eliminate the drawbacks of barrier protection by providing consistent prophylaxis against viral infection for as long as the medication is used and the virus remains clinically susceptible.

Conclusion

As economies reopen, schools resume and passive social distancing becomes more difficult, there is an urgent need for active prophylaxis against COVID-19. PrEP modeled on malaria and HIV/AIDS prevention using readily available and clinically appropriate medication provides the means to fulfill this need in large populations at risk for viral infection. Until a vaccine can be found, PrEP for COVID-19 seems a logical and feasible choice for resumption of work activities and social interaction on a worldwide scale.

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