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VIEWPOINT

COVID-19, hydroxychloroquine and the importance of disease progression

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Abstract

The COVID-19 pandemic struck swiftly and forcefully. The medical response both commercial and clinical achieved what it could with the resources it had. In addition, society changed old habits and developed new behavior patterns. It is appropriate to identify what lessons were learned from COVID-19 for the future. The most important observation for managing SARS-CoV-2 infections was the identification, but not necessarily appreciation, of the manner in which the virus acts over time in the host that it infects. Based on population densities, the ease with which people are mobile and the way that SARS-CoV-2 infected humans, other infectious diseases can easily become pandemics in the future. This review is not focused on a xenobiotic and its toxicant properties. Rather, the review describes the relationship between a therapeutic (hydroxychloroquine) and the progression of a disease (SARS-CoV-2) along with the timing and sequence of the various pathologies that the disease causes. While at first glance, this may appear to beyond the scope of toxicology, it is not. Toxicology is capable to address disease-induced pathologies because it can use the same skills and tools that it uses for pathologies that xenobiotics cause. Assessing the pathology caused by a disease concurrently with the pathology caused by the drug used to treat the disease, puts toxicology in a position to make a greater contribution to drug development. Repurposing toxicology, just as drugs were repurposed for the COVID-19 pandemic, will avoid missing or misusing a useful therapeutic agent just because the disease-initiated pathology was ignored or unappreciated.

Key words: COVID-19, SARS-CoV-2, pandemic, hydroxychloroquine (HCQ)

Introduction

In the first half of 2020, during the early stages of the COVID-19 pandemic, there was a flurry of activity within the medical community to save patient's lives. The response to the pandemic will continue and if we are alert, we will learn something from our experiences. The time is right to assess how important scientific analyses for identifying treatment options for SARS-CoV-2 infections were conducted.

Understanding how SARS-CoV-2 causes pathology in humans and the mechanism by which it initiates and perpetuates the pathology in individual subjects is not going to be found in clinical trials. Investigations assessing treatments in humans tell very little about how a disease condition begins and how it progresses at the micro-physiological and molecular level. Succinctly stated: clinical studies are not conducted for mechanistic insight. Yet, the medical literature about the COVID-19 pandemic in the first half of 2020 was skewed toward epidemiology. By its nature, epidemiology is replete with clinical studies, each of which was a collection of uncontrolled and unmanaged variables through no fault of the investigators, but rather the circumstances that SARS-CoV-2 presented. Epidemiology is the tool of choice for answering what happened but it falls short in addressing how it happened.

Early in the pandemic, clinically oriented studies did not provide the opportunity to address SARS-CoV-2 for what it

is—a toxicant and not a life form. In a functional and operational sense, SARS-CoV-2 is a xenobiotic: non-living material with a chemical structure that is foreign to the host. Most importantly from a toxicological perspective, SARS-CoV-2 elicits its adverse behavior and causes its unwanted effects in a dose–response manner [1].

While clinicians were scrambling to save lives, pharmaceutical companies were focused on a plethora of target-rich opportunities using drugs they had on their shelves. Consequently, epidemiologists were reducing everything the clinicians were attempting to do to graphs and projections as the stocked shelves were exploited. Predictions were flowing in every direction, most of which ended up being inaccurate and inflated. The population at large was looking for what it knew and understood, like testing and vaccines. Mistakes were made, maintaining a focus was difficult and shifting directions were commonplace. Planning and thoughtfulness became an unattainable luxury when the operations rapidly moved into crisis mode. Nonetheless, we learned much but we also overlooked important information.

Early in the response to the SARS-CoV-2 virus, it became clear that the therapeutic targets occurred both within the virus as well as with the human host's response to the virus. Ordinarily, the development of potential therapeutics requires nonclinical toxicology support before the therapeutics have their day in the clinic. In search of therapeutics for COVID-19 pandemic, the approach was different. Candidate therapies were drawn from available drugs, which were developed for treating other diseases. If those therapies had a known toxicity profile, they became repurposing candidates for potential treatments in the COVID-19 pandemic. The identified candidates were immediately sent to the clinic for efficacy investigations and assessments. This repurposing strategy made sense, especially during a crisis pandemic. Yet, there was more interest if a drug worked rather than understanding how a drug worked or why it did not work.

The Culprit: SARS-CoV-2

SARS-CoV-2 is a member of coronaviruses (CoVs), which is the largest group of positive-sense of 5′-3′-single stranded RNA viruses ranging from 26 to 32 kilobases. CoVs, such SARS-CoV, which was seen in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV), which was first reported in 2012 to infect humans but not in the fashion of SARS-CoV-2. CoVs appear periodically and their pathology and ability to infect humans varies. CoVs are harbored in birds, snakes, bats and various other species and remain pathologically silent. However, when animal-harbored CoVs make a zoonotic jump to humans, there is often infectious consequences, which result in clinically observed pathologies in humans to varying degrees. After the zoonotic jump to humans and if there is human-to-human transfer, then there is a high risk for a pandemic [2–5].

The mechanism of infection of SARS-CoV-2 is important for understanding the course of the pathology that the disease takes and the subsequent therapeutic opportunities to interdict the progress of that course. A key step in the SARS-Cov-2 infection and the beginning of the pathological process is the entry of the virus into the host's cells. That initial step of the disease process and the mechanism by which the virus enters the human cell is understood.

The virus has a spike protein structure on its surface that serves as a ligand for the host cell receptor. The ligand spike protein is a glycoprotein trimer (S) that is found in most, if not all coronaviruses. The receptor on the host's cell surface is the angiotensin-converting enzyme II (ACE2), which is ubiquitous in the human host, occurring on many different host cell types. ACE2 serves not only as an attractant for the virus on the host's cell surface, but it also serves to facilitate the entry of the virus into the host's cell. Any interdiction of SARS-CoV-2 entry into the host's cells will be a valuable therapeutic track. More to the point:

> if the virus is prohibited from entering the host's cell, the disease is unable to progress.

The importance of restricting the entry of the virus into the host's cells cannot be overstated.

The SARS-CoV-2 spike protein binds to the human ACE2 receptor more tightly than spike proteins from other corona viruses, including the RaTG13 virus, which is found in bats. SARS-CoV-2 virus, which is believed to have originated in bats, has a genome and sequence similarity that is greater than 93 and 96%, respectively, to the RaTG13 virus. Furthermore, the spike protein of SARS-CoV-2 binds to the ACE2 receptor more tenaciously (1000-fold) than the spike protein from RaTG13 [6, 7]. The strength of the receptor-ligand binding may be why the SARS-CoV-2 infections are intense and persistent, affecting multiple organs.

The way in which the human immune system responds to SARS-CoV-2 appears to be different than the way it responds to other viral and many bacterial infections. In addition, there also appears to be a wide variability of the immune response both within and among individuals. All of the evidence establishes a temporal dimension to the SARS-CoV-2 infection process and subsequent pathologies.

If the direct adverse effect of the virus was not enough to cause serious damage, the host's own defense mechanisms can become the proximate destructive consequence of the viral infection. These host-originated destruction mechanisms, which are intended for invaders to the host, include runaway inflammatory responses, such as cytokine storms and sepsis cascades paving the way for widespread coagulation. When this occurs in the lungs, it results in acute respiratory distress syndrome (ARDS). The pathology caused by SARS-CoV-2, either directly or indirectly (host driven), is not instantaneous. There is a time requirement for the various pathologies to manifest themselves, and consequently, this is further evidence that the disease has a temporal component. This temporal dimension is important for selecting the correct therapy as well as the timing when the therapy is administered. Consequently, clinical studies that measure the effectiveness of a therapy must consider the temporal dimensions of the complete infection process.

Hydroxychloroquine: A Known Entity

Established therapies for immune-related diseases would be good candidates for possible therapies for SARS-CoV-2 infection [8, 9]. One of the repurposed drugs that was considered early in the pandemic for treating COVID-19 was the antimalaria drug hydroxychloroquine (HCQ) [9]. HCQ, in addition to being an accepted therapeutic for malaria for over 50 years, was also repurposed for treating various immunologically rooted diseases such as rheumatoid arthritis and systemic lupus erythematosus because of its ability to mollify the inflammation process [10,11].

This review is not about the toxicity of HCQ. The toxicities, the levels at which those toxicities are evident and the subsequent human health risk assessments of HCQ have been determined for its previous uses in therapeutic settings. Attempts at adding

knowledge to the half-century human experience with HCQ as an effective therapeutic is less productive than extracting what we know about HCQ in order to do a better job at developing new drugs. Toxicology not only can assist in developing new drugs, but also there is a way toxicology can help in making new drugs more effective. The subject of this review is the relationship of HCQ to the time course of the various pathologies that result from a SARS-CoV-2 infection.

In addition to being an established therapy for malaria and immunologically based diseases, the mechanism of HCQ's inhibition of SARS-CoV infection has been established and its effectiveness in inhibiting its spread has been well documented [12, 13, 14, 15, 16]. The *in vitro* efficacy has never been questioned not only from the data generated in several laboratories but also by the fact that the mechanism of HCQ's inhibition is understood and explainable. Consequently, clinical investigations with HCQ were initiated on patients who were infected with SARS-CoV-2 [17].

HCQ received intense attention in all venues, such as basic medical science, clinical investigations and the lay press. While the attention was broad and widespread, the clinical investigations could not be planned or protocol driven and, therefore, had a high propensity for inaccuracies. The most notable inaccurate assessment of HCQ was the point in the disease where it acted as an effective therapeutic agent. Consequently, significant attributes of HCQ were overlooked, unappreciated or purposefully ignored in the hodgepodge of clinical studies where HCQ was assessed for efficacy.

The short shrift paid to the analyses of the HCQ clinical investigations and the demonization of HCQ in the lay press has both a negative consequence and a beneficial dimension [18]. The negative consequence was that many infected people did not receive benefit from the proper HCQ treatments, and it is likely some unknown number of people died. The beneficial dimension of the clinical studies was that the timing of HCQ dosing brought into focus the importance of aligning the therapeutic treatment schedule with the course that the infection takes.

HCQ: Effective for Avoiding SARS-CoV-2 Pathology

The results from the clinical studies with HCQ were mixed. This was a surprise at the time since the mechanism of HCQ's inhibition of SARS-CoV-2 was recognized, understood and the *in vitro* effectiveness against SARS-CoV-2 virus was demonstrated [12, 14, 17]. Some clinical trials indicated that HCQ reduced mortality while other studies showed no effect. The inconsistent picture resulted in confusion. The confusion was exacerbated by many factors such as the inability to control clinical variables, protocol inconsistency, the application of sophisticated and rigorous standards for interpreting clinical studies, which resulted in rigidity rather than in reasoned judgment. Even politics exacerbated the confusion and misunderstanding [18]. These confusing and contradictory results had an adverse effect on policy guidance, clinical practice and, most significantly, caused patient suffering and death.

In spite of the clinical mishmash on HCQ, there was a lucid moment of penetrating insightfulness. Risch [19] identified the problem: "HCQ + azithromycin has been widely misrepresented in both clinical reports and public media ..." Risch went on to provide the needed clinical guidance: "... hydroxychloroquine + azithromycin in *inpatients*, is irrelevant concerning efficacy of the pair ... [when compared to] early high-risk *outpatient*

disease" *[emphasis added]*. Essentially, Risch was advocating the prophylaxis potential and use of HCQ in preventing COVID-19 and its early progression in *outpatients* rather than treating COVID-19 once the disease established a foothold in *inpatients* who had to be admitted into hospitals. The value Risch adds to the SARS-CoV-2 story is the articulation of the importance of the course the disease takes in the context of a therapeutic treatment schedule. In another words, the progress of a disease is important as to when a drug is administered. Risch directly confronts the temporal component of SARS-CoV-2 pathology.

Arshad et al. [20] support Risch's advocacy: "The benefits of hydroxychloroquine in our cohort as compared to previous studies maybe related to its use early in the disease course ...". It is significant to note that when the pandemic was first recognized, Million et al. [21] hinted that HCQ treatment early in the course of COVID-19 may be effective: "Administration of the HCQ + AZ [hydroxychloroquine + azithromycin] combination before COVID-19 complications occur is safe and associated with a very low fatality rate in patients."

The Arshad et al. study [20] is a particularly important for two scientific reasons. The first important scientific reason is that the Arshad et al. [14] study validates Risch's advocacy [19] and confirms Million et al.'s [21] initial work. During these times when replication of many scientific studies cannot be accomplished, the replication is noteworthy that HCQ's efficacy was confirmed in three independent investigations. This replicability of HCQ's efficacy was accomplished in spite of an incredible number of known and unknown variables. The one consistency for all three assessments of clinical efficacy was that the administration of HCQ was done early during the course of the infection. Consequently, the progression of the disease cannot be ignored.

This stunning achievement of the troika (Risch et al., Arshad et al. and Million et al.) was not only unrecognized but it was also unappreciated. On the surface, it is difficult to understand how the remarkable science accomplished by the troika was and is ignored. Nonetheless, it is important to see how their accomplishment was missed. Seeing, recognizing and correcting mistakes is virtuous; not correcting mistakes is a flaw.

Approximately, a month after the peer-reviewed Arshad et al. study was published, the Director of the National Institute of Allergy and Infectious Disease (NIAID) whose role is to inform and advise on health policy, testified before the *Congress U. S. House Select Subcommittee on the Coronavirus Crisis* [22]. The NIAID Director told the Subcommittee that the Arshad et al. study was flawed because it did not meet the "gold standard" of clinical studies in so far it was not a randomized, placebo-controlled study. This "flawed" study showed a twofold increase in survival (13 vs 26%). At a minimum, these results deserve a second look. The qualitative aspects the Arshad et al [20] study was predicted by Risch and consistent with the Million et al.'s results. Furthermore, the placebo group of a placebo-controlled study, which is advocated by the NIAID Director, results in an ethical conundrum when the endpoint is death reduction. It is reasonable to believe that individuals infected with SARS-CoV-2 would rather avoid death than be part of a study that meets the "gold standard" criteria.

The second scientific reason that the Arshad et al. work is important, in addition to validating Risch's clinical insight and confirming Million et al.'s initial work, is because the three independent, but identical conclusions lay bare the gaping hole in how treatments for diseases, specifically how viral diseases should be approached in the future. Have we learned anything for addressing the next viral pandemic? Maybe, a clinical trial is not the universal answer to addressing viral infections.

The important issue in a SARS-CoV-2 infection is the time-course progression of a disease. It is a more important factor for determining a treatment course than the results from a clinical trial that is a randomized, placebo-controlled study but insensitive to how and when a disease progresses. It is ironic that using the results from a "gold standard" tool results in practicing medicine as a discipline rather than addressing a disease and treating and curing patients.

For whatever reason, the Scientific Medical Policy Committee of the American College of Physicians (Committee) has not recognized the temporal dimension of SARS-CoV-2 pathology nor have they acknowledged the benefits of HCQ as a prophylactic measure or its use early in the disease process [23]. The standing Committee addressed clinical practice guidance for practicing clinicians by asking the following question:

> Should clinicians use chloroquine or hydroxychloroquine alone or in combination with azithromycin for the prophylaxis or treatment of COVID-19?

In response to their own question, the Committee responded with three "Practice Points," which essentially are recommendations for practicing physicians. In summary, the Committee recommends against using HCQ for either the prevention or treatment of SARS-CoV-2 infections and if physicians choose to administer HCQ to patients, they should do so for only those patients who are enrolled in a clinical trial and have tested positive for the virus. It is clear that the nine-member committee does not appreciate the significance of the progression of the SARS-CoV-2 viral disease and the *in vitro* antiviral literature, including the mechanism of HCQ in restricting the virus from entering the host's cells. Furthermore, the Committee has not read a report in the same journal in which their "Practice Points" were published, which states [24]:

> Hydroxychloroquine and chloroquine have antiviral effects, in vitro against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

The Committee is not alone. The World Health Organization (WHO) continued to ignore the important temporal dimension in the SARS-CoV-2 infection. WHO published results that they claim show that remdesivir, hydroxychloroquine, lopinavir and interferon were ineffective treatments. Unfortunately, the drugs were used in hospital for inpatients who were well down the disease path, showing serious signs of morbidity. It was obvious that the time course of the disease was not considered and no distinction was made by WHO between disease prevention versus disease treatment [25].

Future clinical investigations on HCQ must be conducted on patients before they require admission into the hospital, preferably after testing positive but asymptomatic. A second group of potential clinical subjects are those who show symptoms but whose symptoms are not severe enough to require hospitalization. Using asymptomatic outpatients and outpatients showing mild symptoms, the SARS-CoV-2 disease's inflection point for maximal HCQ efficacy may be defined. Such an approach for a clinical investigation was suggested by Avidan et al. [26]

With COVID-19, there has been if not a lack of understanding at least a lack of appreciation of the importance of the time-course of the disease caused by SARS-CoV-2. The time course of a disease itself within individuals (disease dynamics) is as important, perhaps even more important, than the time course of the disease in a population (epidemiology), or the time course of drugs to treat the disease (pharmacokinetics). There is an opportunity during the COVID-19 pandemic to step back and assess whether or not a shift in reference point would be beneficial. For example, for some time, medicine has been considering and assessing the concept of Personalized Medicine wherein treatments for a specific disease or pathologies are tailored for a group or class of patients. It is possible to change the focus, when appropriate or necessary, to reorient the attention from individual groups or classes of patients to the specific disease.

Conclusions

The conclusion that HCQ is not effective in treating SARA-CoV-2 infections is based on retrospective epidemiology studies that failed to meet the "gold standard" criteria by not being randomized and placebo controlled. It is mindless groupthink to use "goal standard" criteria to analyze responses from patients whose disease condition had passed beyond the point when HCQ would have been a beneficial therapy. Rather than asking the question of whether or not HCQ is an effective **treatment**, the question should have been whether or not HCQ effectively **prevents** serious adverse events from a SARS-CoV-2 infection.

In order to be true to the practice of medicine and give credible information to policy makers, it has to be recognized that the objective is not to practice a discipline but to save lives. There is sufficient evidence that HCQ is safe and effective if it is given early in the SARS-CoV-2 infection.

Understanding how a disease progresses, knowing the various stages of the disease and when they occur is a requirement for selecting the correct drug and the correct timing of the dose of the drug. Yet, to a large extent, this was and still is ignored in SARS-CoV-2 infections. Attention to the time course of a disease, any disease, avoids missing important drug targets and any shifts that a disease may take during its pathological path. As an example, there was an inordinate attention given to the cardiovascular toxicity of HCQ at the expense of inattention as to when in the progress of the infection the administration of HCQ would be most effective. The important generic lesson that SARS-CoV-2 taught was that the progression of a disease is just as important for identifying pathologies in the host as the pathologies that result from administered therapeutics.

So, has the toxicology profession learned anything? Without any doubt, toxicology learned about an important discipline-expanding opportunity: toxicology can be expanded in the drug development arena beyond its previous role as a service function. Historically, toxicology has contributed to drug developments by identifying drug toxicities, the levels at which they occur, the levels when toxicity is absent and based on the therapeutic levels, the risks associated with the drug. What has been absent from that historical picture is the pathology caused by the disease for which the drug is intended to treat. Concurrently assessing the pathology caused by a disease over time along with the toxicokinetics and toxicodynamics of the drug used to treat the disease, positions toxicology to make a greater contribution to drug development. Repurposing toxicology to include pathologies initiated by disease, not just diseases caused by viruses, will enrich the drug development process. Just as drugs were repurposed for the COVID-19 pandemic, expanding toxicology's role to include disease-initiated pathology will avoid missing or misusing a useful therapeutic agent just because the disease-initiated pathology was ignored or unappreciated.

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